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THIRD SERIES FOUNDED BY EDWARD JACKSON

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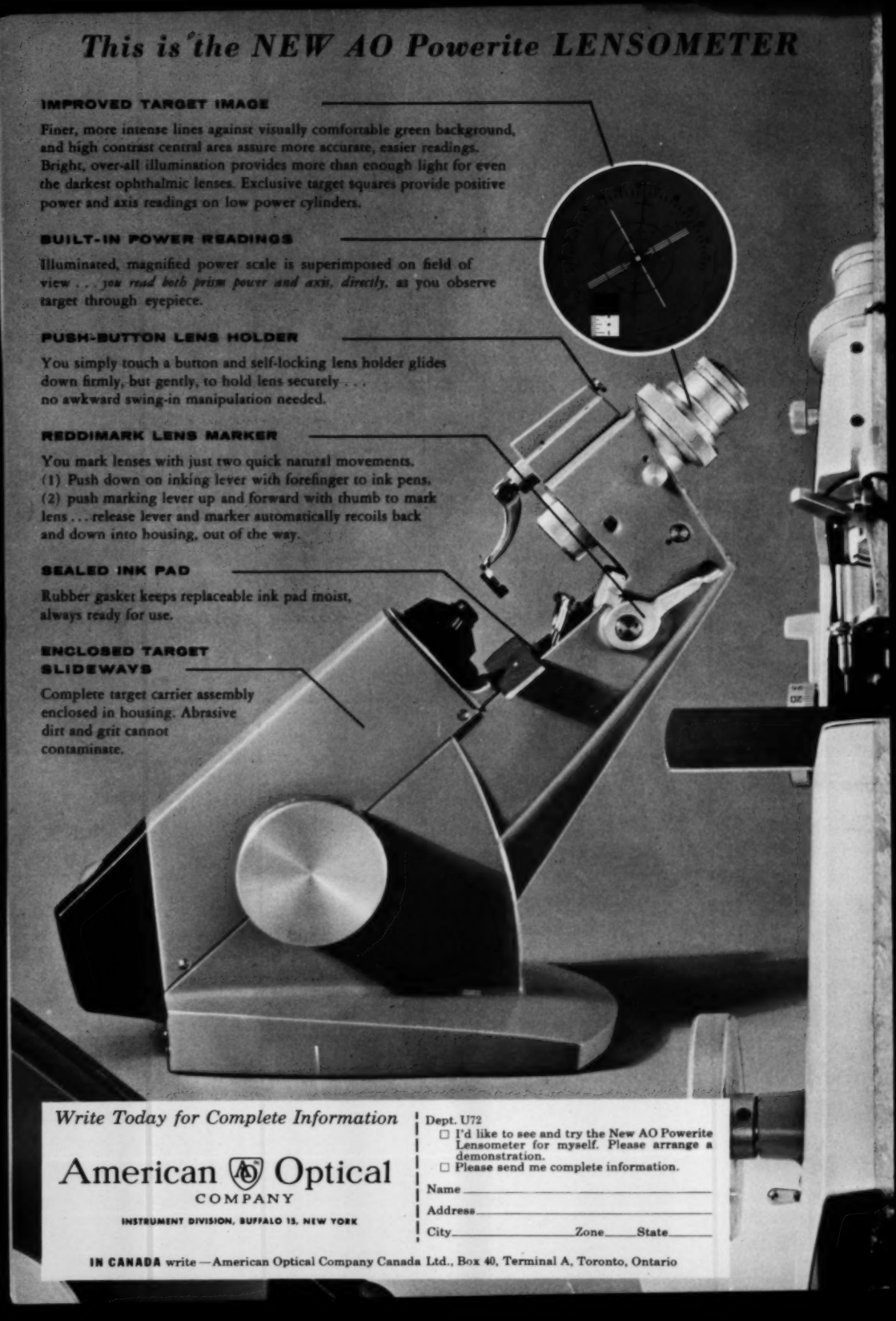

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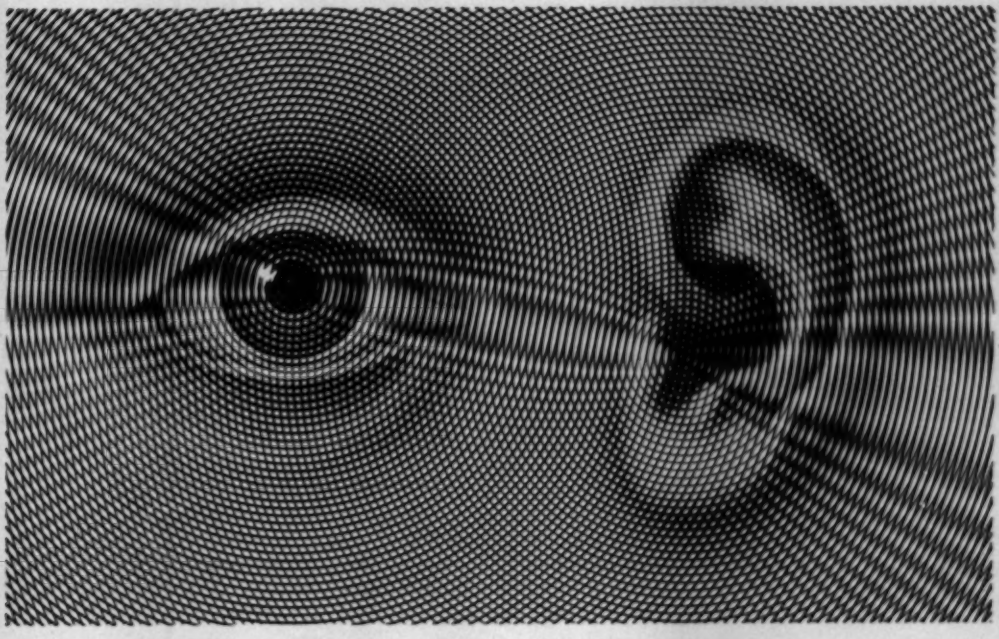

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*Witten, V. H.; Sulzberger, M. B., and Arthur, G. W.: *Clin. Pharmacol. & Therap.* 1:294 (May-June) 1960.

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1. Gordon, D. M.: Scientific Exhibit, American Medical Association, Annual Meeting, San Francisco, 1958.

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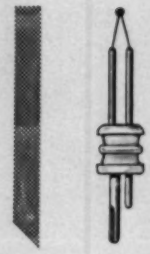

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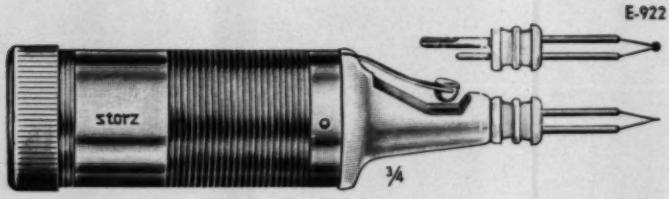

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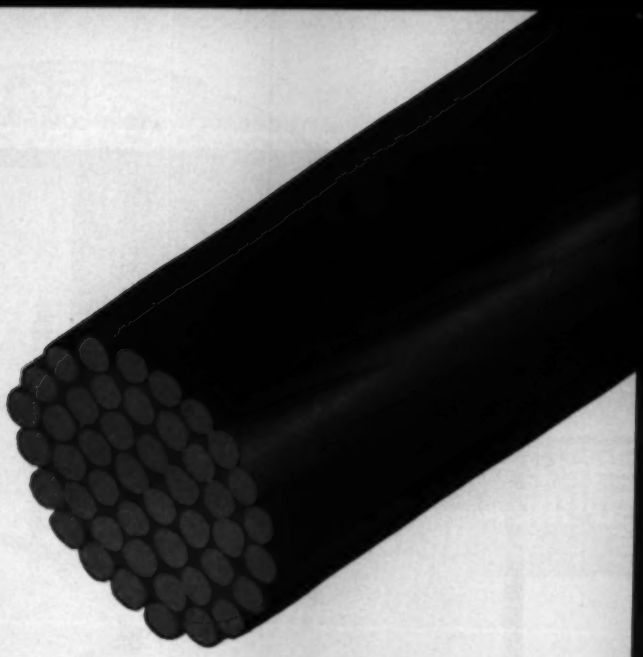

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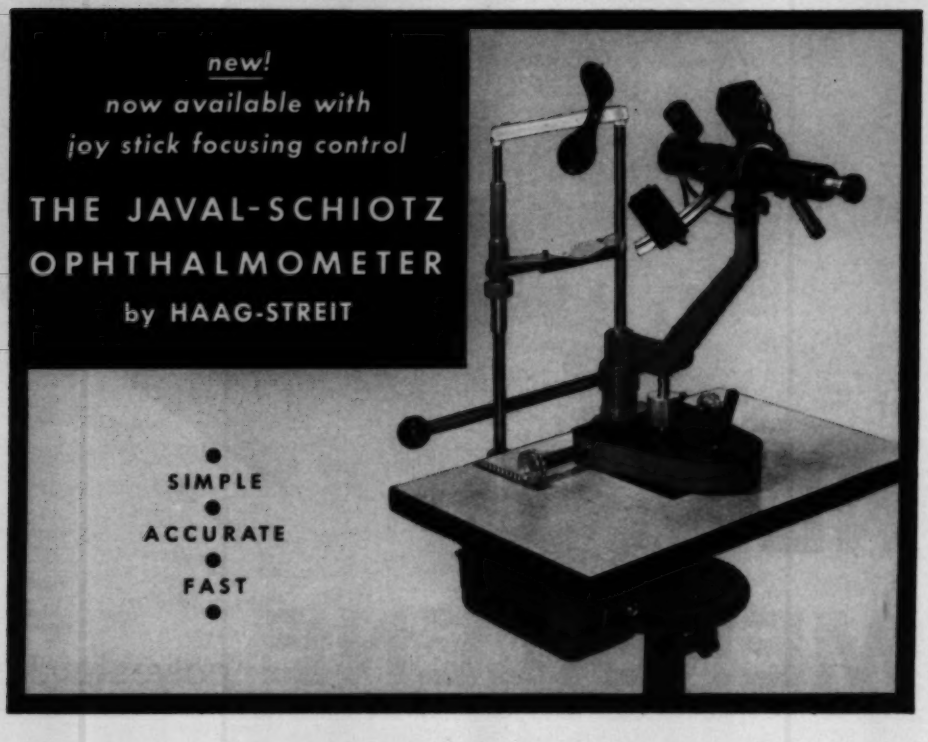

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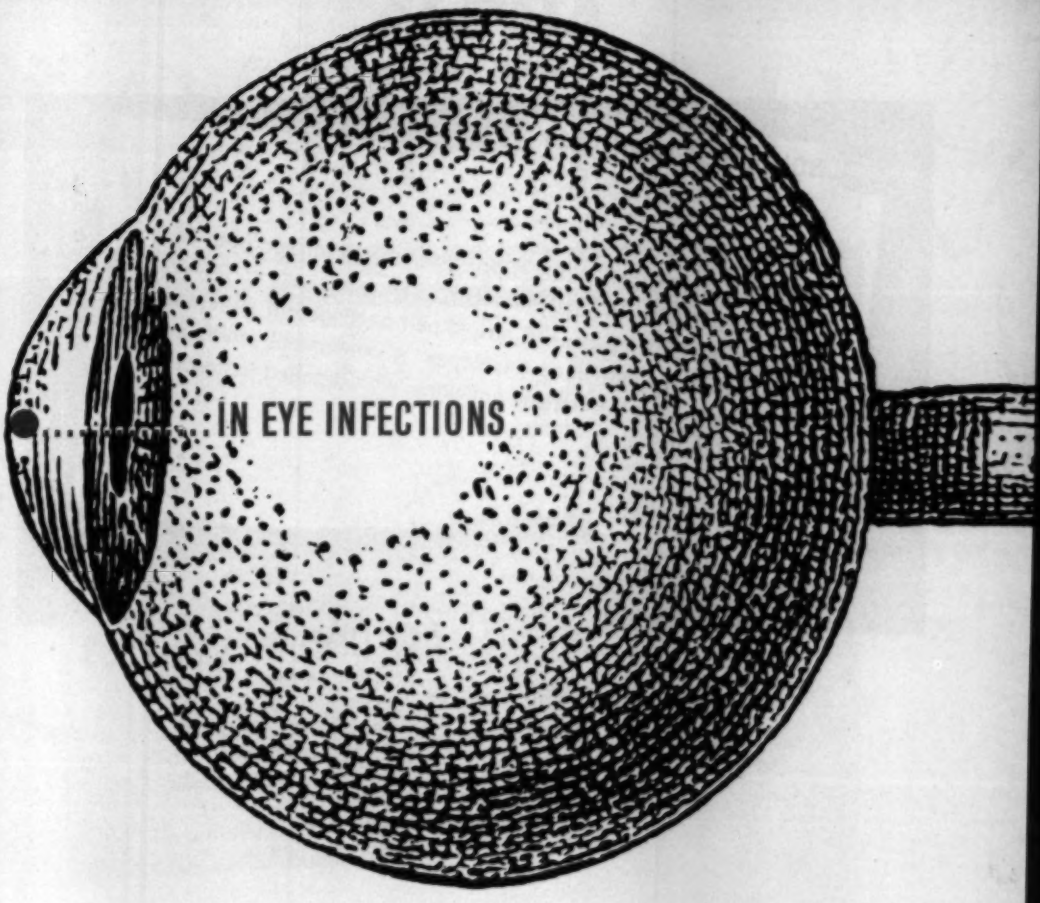

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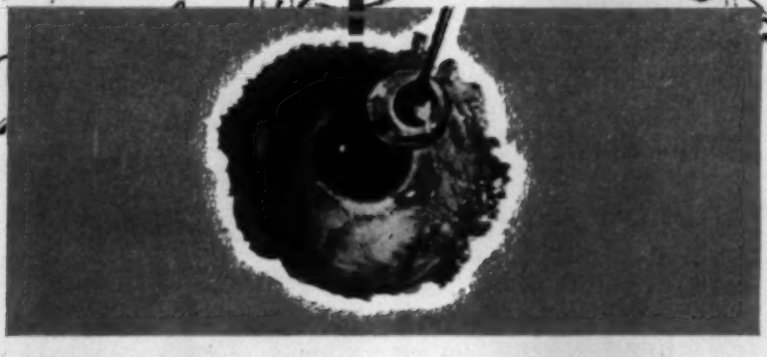

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1. Thorpe, H. E.: Am. J. Ophth. *49*:531-547 (Mar.) 1960. 2. Schwartz, B., *et al.*: Tr. Am. Acad. Ophth. & Otol. *64*:46-54 (Jan.-Feb.) 1960. 3. Cogan, J. E. H.: Proc. Roy. Soc. Med. *51*:927, 1958. 4. Jenkins, B. H.: J.M.A. Georgia *45*:431, 1956. 5. Raiford, M. B.: J.M.A. Georgia *48*:163, 1959. 6. Rizzuti, A. B.: Arch. Ophth. *61*:135, 1959.

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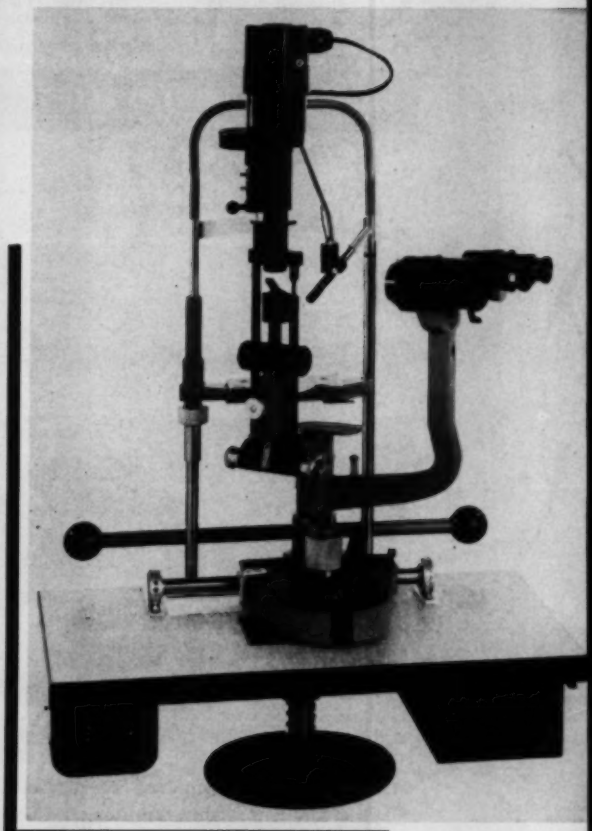

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[1] CLIFTON, C. E. AND HALL, N. C. "RE-STERILIZING ACTIVITY OF CERTAIN CONTACT LENS SOLUTIONS." CONTACTO, THE CONTACT LENS JOURNAL, 3:10, 301-3, 1959.

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*Fleming, T. C., and Merrill, D. L.: Comparative Corneal Penetration of Water Soluble and Non-water Soluble Corticosteroids: Presented at 108th meeting, American Pharmaceutical Association, Aug. 19, 1959.

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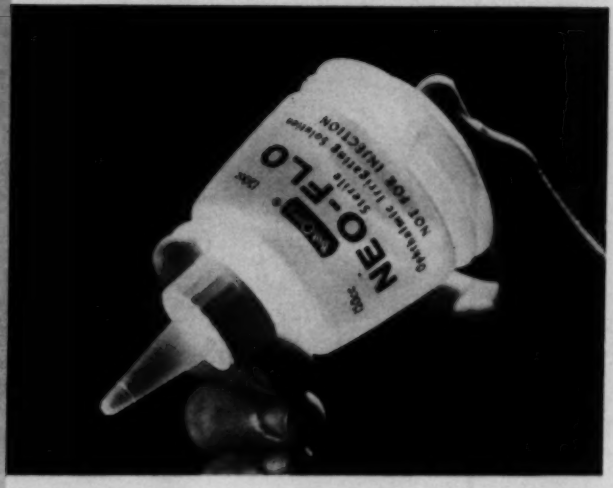

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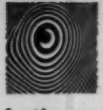

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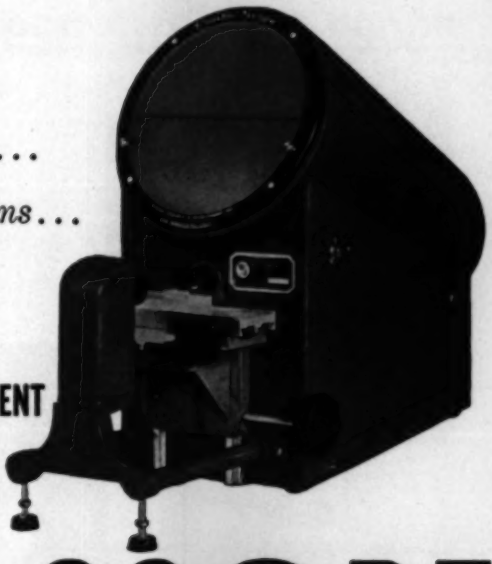

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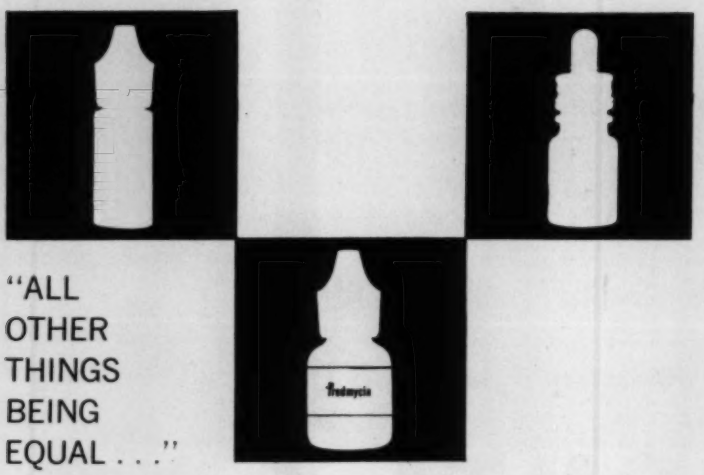

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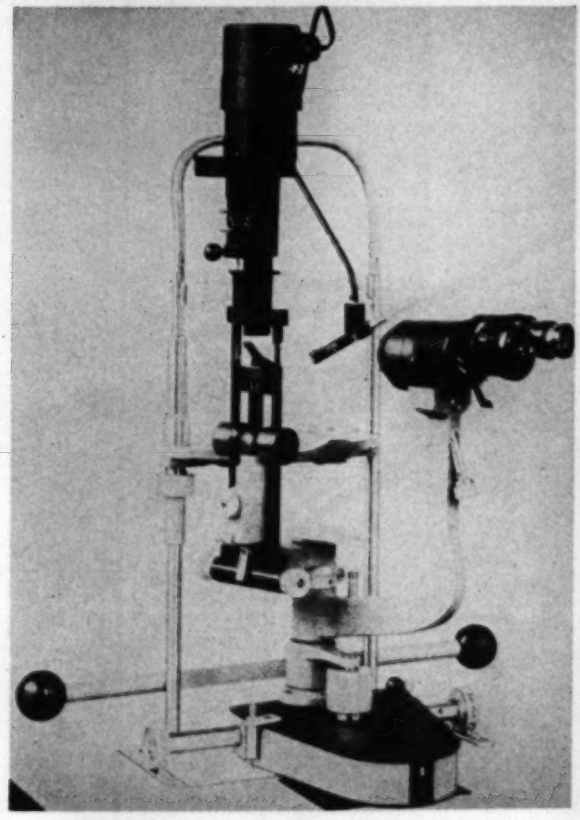

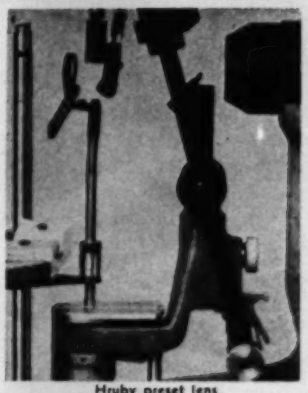

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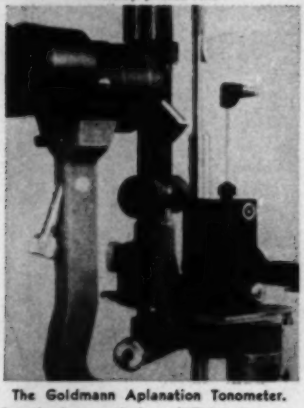

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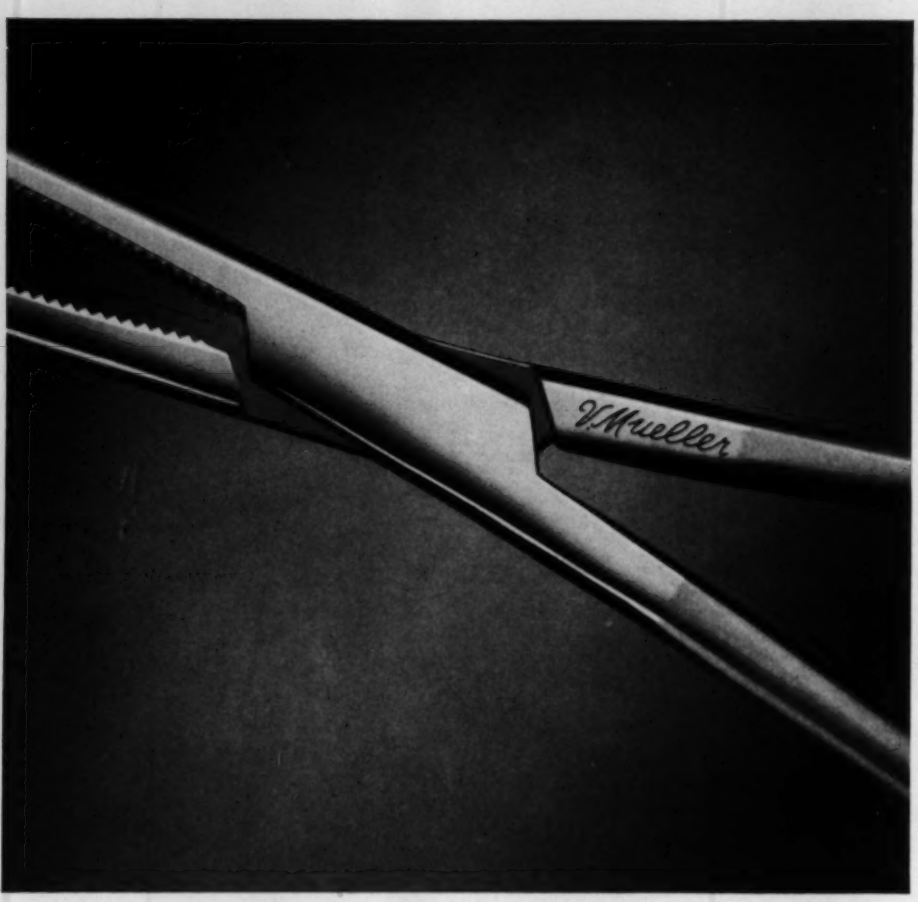

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1. *Am. J. Digest. Dis.* 22:5, 1955.
2. *M. Times* 84:741, 1956.
3. *Am. J. Ophth.* 42:771, 1956.
4. *Southwestern Med.* 40:120, 1959.

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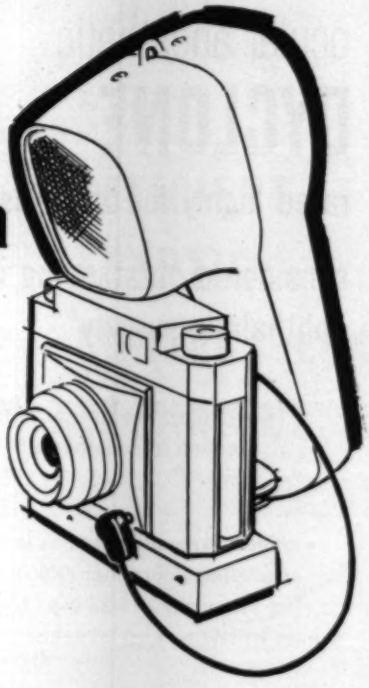

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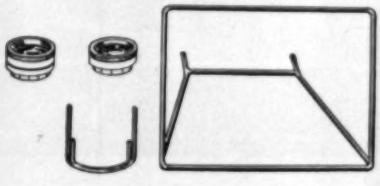

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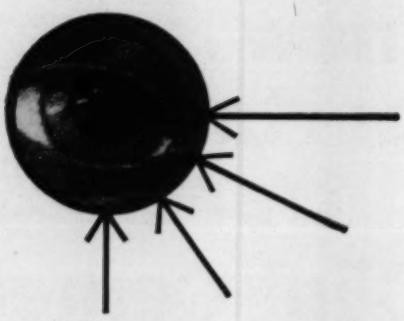

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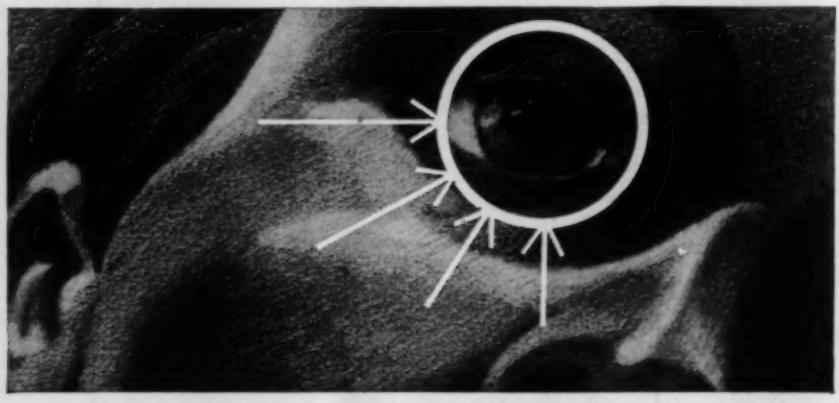
1. Swan, K. C.: Tr. Am. Acad. Opth. *60*:368, 1956.
2. Arora, R. B., et al.: E. E. N. T. Monthly *34*:593, 1955.
3. Florestano, H. J., and Bahler, M. E.: J. Am. Pharm. A. (Scient. Ed.) *45*:360, 1956.



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- Irrigate eyes with CONTOSE Sterile Irrigating Solution to cleanse them of dried secretions and mucus . . .
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- Wet and cleanse lenses by rubbing thoroughly with a liberal quantity of CONTACTISOL® sterile Wetting Solution, then rinse off with CONTOSE . . .

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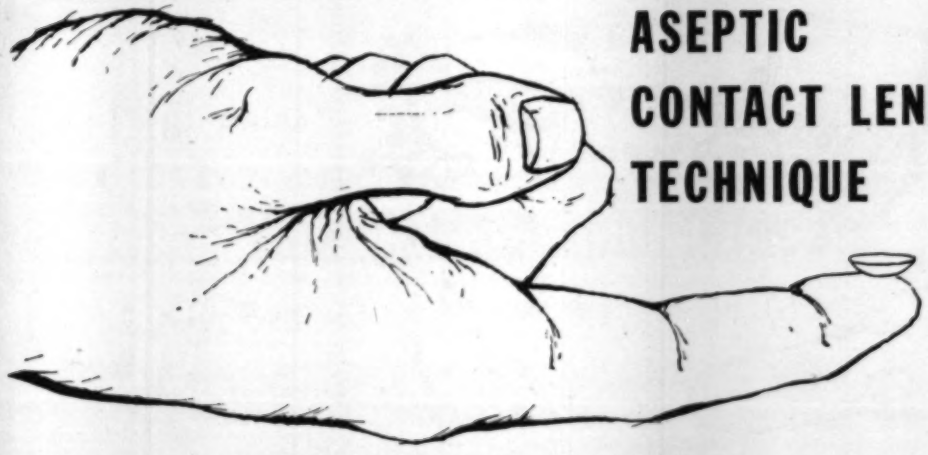

- Now, insert the moist lenses. When removing lenses, wash and thoroughly rinse hands, refill the soaking chamber with VISTEX® Sterile Soaking Solution, then . . .
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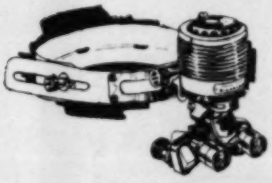

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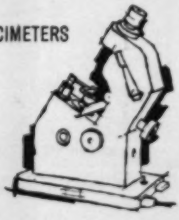

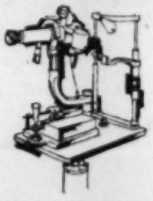

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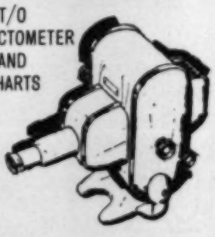

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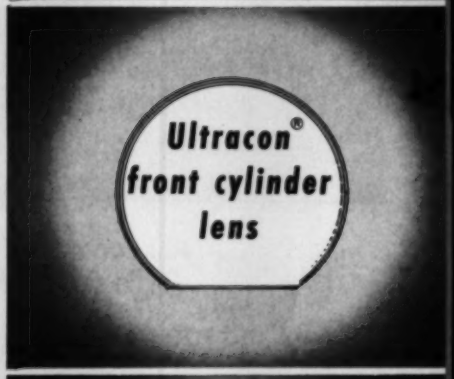

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CATARACT CENTERING

In a strong correction, chromatic aberration can occur in the distance portion of a bifocal as well as in the segment.

We have the history of Mrs. S. who is a monocular cataract case. She has very good vision in the operated eye and little or no vision in the other eye. The aphakic eye requires + 11.50 on + 3.00 axis 175 with + 3.00 add for reading.

This correction gave excellent near and distance vision but, with the bifocal lens, the patient complained at once that everything she looked at was tinged with blue. Surprisingly, objects viewed through the distance lens were just as blue as those seen through the bifocal segment.

An examination of the lens revealed no grinding defects. The surfaces were well polished and the correction and axis were perfect. However, a check of the centering revealed that when the patient looked straight ahead the optical center of the lens was 3 millimeters off the visual axis. This poor centering resulted in 6 prism diopters of error.

Before making a new lens for Mrs. S. this prism was neutralized by placing a 6 degree prism base in over the lens to offset the 6 degree error which was base out. The patient reported immediately that the blue cast was gone.

A new lens, perfectly centered, was made and the patient reports no chromatic aberration whatsoever.

Cases like this point up the fact that proper centering is just as important in monocular fitting as in binocular fitting. Too often, badly centered lenses are passed on to the patient with the false justification that since only one eye was being used the centering was of no importance.

"if it's a lens problem, let's look at it together"

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AMERICAN JOURNAL OF OPHTHALMOLOGY

SERIES 3 · VOLUME 50 · NUMBER 4 · OCTOBER, 1960

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ABSTRACTS

Ocular motility; Conjunctiva, cornea, sclera; Uvea, sympathetic disease, aqueous; Glaucoma and ocular tension; Crystalline lens; Retina and vitreous; Optic nerve and chiasm; Neuro-ophthalmology; Eyeball, orbit, sinuses; Eyelids, lacrimal apparatus; Tumors; Injuries; Systemic disease and parasites; Congenital deformities, heredity; Hygiene, sociology, education, and history 673

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1. Gordon, D. M.: **Am. J. Ophth.** 47:536, April, 1959.

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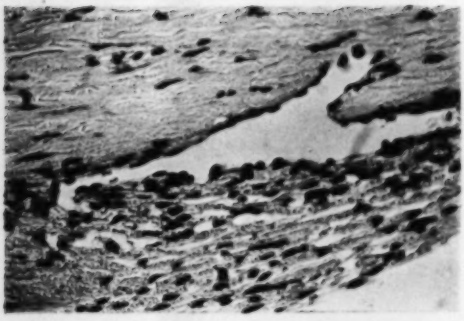

Fig. 2

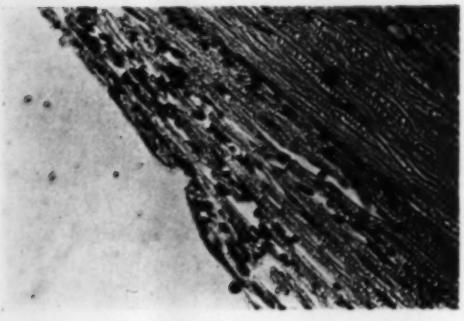

Fig. 8

Figs. 2 and 8 (Theobald). The limbal area: With particular reference to the trabecular meshwork in health and disease.

Fig. 2. High-power view of Figure 1, showing Sondermann inner canal and blood in the intratrabecular spaces.

Fig. 8. This photomicrograph shows obliteration of the lumen of Schlemm's canal due to hypertrophy and sclerosis of the trabeculae and the overlying sclera. The scleral fibers are hyalinized as well as hypertrophied. Some pigment cells are seen between the trabeculae. (From Theobald, G. D., and Kirk, H. O.: Am. J. Ophth., 41:11-21, 1956.)

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THE LIMBAL AREA*

WITH PARTICULAR REFERENCE TO THE TRABECULAR MESHWORK IN HEALTH AND DISEASE

THE XIV FRANCIS I. PROCTOR LECTURE

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Oak Park, Illinois

PART I

To be chosen to deliver the XIV annual Francis I. Proctor Lecture is an honor which I deeply appreciate and humbly accept in my own name and proudly accept in the name of all women who have—or are—practising medicine and especially those women physicians who have chosen the specialty of ophthalmology.

Although I did not know Dr. Proctor personally, I know and have known a number of his followers. It has been said that the life of a great man continues in the achievements of his disciples. That Dr. Proctor's influence will remain alive through many generations is attested by the contributions of the great ophthalmic institute which bears his name.

The subject I have chosen for the XIV Francis I. Proctor Lecture, "The limbal area: With special reference to the trabecular meshwork in health and disease," is one which I approach with trepidation for I have few recent original observations to contribute to the subject which I shall discuss. Moreover, within the last couple of years the Francis I. Proctor Laboratory has reported some remarkable research, utilizing the advanced technique of electron microscopy, which has contributed to our knowledge of the anatomy and physiology of the tissues of the intercalary portion of the eye which ophthalmologists are accustomed to designate as the limbus.

The importance of the limbus is based on its function as an outflow area for the aqueous humor. To refresh our minds on the anatomic structure of the limbal area, let us turn to the pages of Fuchs' textbook to learn that the limbus is at the periphery of the cornea where the conjunctiva ends in a sharp edge; the conjunctiva sclerae is loosely adherent to its substratum.

The tissues of the sclera and cornea are very much alike, and moreover at the corneal margin pass into each other without sharp line of demarcation. They are chiefly distinguished by the arrangement of the fiber bundles which are more regular in the cornea than in the sclera.

Enough for the textbook anatomy. To the laboratory worker, the limbal area means a two-mm. area the entire thickness of the scleral side of the corneoscleral junction; and the corneoscleral junction is an imaginary line drawn from the end of Bowman's membrane to the end of Descemet's membrane. In this area are four plexuses of vessels, the anterior three of which have to do with nourishing of the cornea. They are (1) the conjunctival plexus in which the arteries and veins become engorged in conjunctival inflammation and superficial keratitis; (2) the episcleral vessels which, in fact, are in Tenon's capsule, are also involved in

* Presented at the University of California Medical Center, San Francisco, December 4, 1959.

severe superficial keratitis; (3) the intrascleral vessels which cannot be seen clinically except in deep keratitis when the vascular branches form broom-straw vessels in the depths of the cornea; (4) the fourth plexus is the one connected with Schlemm's canal and is known as the deep intrascleral plexus. These four plexuses anastomose with each other more or less freely.

It was only after the slitlamp was invented that it was possible to detect the fine vascular loops adjacent to the cornea. Vogt in his *Atlas of Slitlamp Microscopy* took great pleasure in describing the fine capillary loops at the corneoscleral junction. Among other things he notes:

"The greater part of the vessels of the limbal zone of the normal eye, when at rest, contain no blood. Often we may see vessels that at times contain short columns of blood, again they are empty. . . . On irritation of an area, by rubbing with the eyelid, the following observations have been made: For a few seconds there is no change, then the vessels gradually fill with blood. If the massage is sufficient, the whole capillary network which was heretofore invisible appears in a distinct manner, as if it were injected with an artificial coloring matter."

So much for the slitlamp appearance of the blood supply of the limbal area—that two-mm. area the entire thickness of the scleral side of the corneoscleral junction—the imaginary line drawn from the end of Bowman's membrane to the end of Descemet's membrane.

In the normal eye, this area can be divided into four layers: (1) the conjunctival layer which is placed loosely over the (2) episcleral layer; (3) the scleral tissue; and (4) the trabecular meshwork.

It is this fourth layer—the trabecular meshwork at the angle of the anterior chamber—which is not only the most important of the four layers of the limbus but in many respects is one of the most important structures in the eye.

The trabecular meshwork lining the anterior portion of the angle of the anterior chamber, is known by many names: pectinate ligament, spaces of Fontana, sclerocorneal trabeculae, scleral and uveal meshwork, cribriform ligament, and so forth.

Of these many designations, trabecular meshwork is the one now in most general use.

The trabecular meshwork has two functions: (1) Its spaces permit passage of aqueous humor from the anterior chamber into the canal of Schlemm; and (2) its fibers form a ligament for the ciliary muscle.

On section, the trabecular meshwork is triangular. Its apex lies in the cornea, just anterior to the end of Descemet's membrane. The meshwork widens posteriorly; the outermost trabeculae insert into the scleral spur, and the innermost trabeculae form the ligament for the ciliary muscles.

It has been observed that contraction and relaxation of the circular fibers of the ciliary muscle cause a widening and narrowing of the intratrabecular spaces and possibly cause a pumping action to facilitate the outflow of aqueous. The trabecular meshwork is a fenestrated structure. Its appearance on cross section has been likened to "wovenwork" and to "sponge pores." There are many openings large enough to admit one to four blood corpuscles into the intratrabecular spaces from the anterior chamber.

The three-dimensional qualities of these openings and spaces are difficult to hold in mind during microscopic study. But it is only by so doing that one can get a true picture of this labyrinth of aqueous pathways.

In 1910 Virchow reported that the trabecular meshwork consisted of a scleral meshwork, or corneoscleral trabeculae, which is the outer portion connected with the scleral spur; and the uveal meshwork, or rudimentary pectinate ligament, which is the inner portion terminating in the ciliary body and iris root (Ashton, 1956).

In a recent study (1954) Burian, Braley and Allen, while agreeing with Virchow's

subdivision, described four groups of trabecular fibers, three of which had attachments to the uveal tract, one group having an inconstant posterior termination. In some instances all of the fibers passed into the tip of the scleral spur; in others, a third to a half of the fibers merged with the connective tissue surrounding the meridional fibers of the ciliary muscle.

According to Salzmann (1912) the meshwork forms a three-sided prismatic band: Anteriorly, the edge is extremely sharp and unites with Descemet's membrane and the adjacent corneal lamellae. Posteriorly, trabeculae extend to unite with the scleral spur, the anterior surface of the ciliary body, and indirectly with the root of the iris. The outer surface borders directly upon corneal and scleral tissue and upon the inner wall of Schlemm's canal or the loose tissue surrounding it. The inner surface is free and is in contact with the aqueous humor of the anterior chamber.

Ashton (1956) refers to the work of Busacca, François, Troncoso, Burian, Kronfeld, and others on the gonioscopic appearance in the area of the meshwork and describes the trabecular band and the ciliary band, as seen gonioscopically. Ashton (1956) then goes on to describe the shape and orientation of the fibers and remarks that "whereas the shape, limits, and subdivisions of the trabeculae have, in general, been accepted by all authors, two different opinions have been expressed concerning the shape and orientation of the fibers themselves."

Early authors came to the conclusion that the flat bands of tissue in the scleral meshwork are predominantly circular in arrangement, that is to say parallel to Schlemm's canal; later authors seem to imply that the meshwork is formed of anteroposterior rods.

We find, therefore, from the descriptions of many authors that the trabecular meshwork begins in the posterior layer of the cornea just anterior to Descemet's membrane and fans out posteriorly, part of the fibers ending in the scleral spur and part entering the ciliary body to become the ligament for the radial and circular muscle bundles.

Recently, Vrabec has written that "as the corneal endothelium approaches the periphery it passes over the margin of Descemet's membrane into the trabecular meshwork where its cells undergo a transition in shape in that they become elongated in the meridional direction. The cement substance often increases in thickness and may cover the whole surface of the cells with a thin argyrophil layer; this cement might possibly aid in the flow of aqueous fluid over this area."

In 1958, Garron, Feeney, Hogan and McEwen by electron microscopy concluded that the cells of the endothelium lining the inner wall of Schlemm's canal differ somewhat from the cells covering the trabeculae. The cytoplasm of the canal cells contained one or more giant vacuoles which often gave them a "signet ring" appearance. The vacuolated space within the cells appeared to be devoid of material opaque to electrons.

Summarizing a recent study by Unger and Rohen (1958) we learn that there are three different tissue formations in the trabecular meshwork integrated into a functional unit:

1. An elastic network representing the mechanical bases of the trabeculae. This reticulum is capable of expansion or contraction.

2. A system of endothelial cells which is continuous from the cornea through the trabecular system, Schlemm's canal and to the iris.

3. Light microscopically homogenous substances enveloping the elastic fibers and forming flat lamellas.

These authors refer to the work of Graumann and Rohen who described (a) a central ground substance lamella, and (b) a superficial subendothelial basement membrane (termed by them a glass membrane) which communicates with another basement membrane situated between Descemet's membrane and the corneal endothelium, and sup-

pose the existence of an "endothelial basement membrane system" for which laws similar to those for the walls of the capillaries may be valid.

Unger and Rohen believe that the two sets of tissue most important to aqueous circulation are the (1) endothelium and (2) the "glass" basement membrane. They conclude that the endothelium is capable of vital storage and hence ought to be designated as retothelium. The cells are able to increase, multiply and desquamate and are thus capable of producing structural alterations. The "glass" membrane, comparable to a basement membrane, can react by an increase of substance.

In 1958 Garron, Feeney, Hogan and McEwen, in reporting their initial electron microscopic study of the human eye, described a mountage of a 70μ by 65μ area of trabecular tissue bordering on Schlemm's canal. They preface their observations by quoting Salzmann's classical description which separates the individual trabeculae into four elements (1) collagen core, (2) elastic fibers, (3) glass membrane and (4) endothelial covering, and go on to say that they could confirm Salzmann's four-component arrangement of a trabecular fiber only so far as the collagen core and the outer endothelial covering were concerned.

Garron, Feeney, and Goldberg compared thin sections of human trabecular material, stained and viewed by phase microscopy, with the findings of electron microscopy. These studies suggested that the scleral meshwork "fibers" do not possess a Descemetlike layer beneath the endothelium nor an elastic tissue layer outside the collagen core. Standard staining techniques for the identification of elastic tissue also stain a nonelastic material outside the collagen core. This material was unknown until recent studies by electron microscopy showed it to be present.

In recent years, too, there have been some most interesting studies on the innervation of the trabecular system of the chamber angle.

In 1954 Vrabec made a systematic search for nerve fibers in the corneoscleral and uveal trabeculae of human and animal eyes and identified a rich network of fibers with sensory nerve endings between the layers of the trabecular system. He was able to trace the fibers back to the ciliary body or the supraciliary space.

Holland, von Sallmann and Collins reported, in 1956, their studies on the innervation of the chamber angle in four classes of vertebrate eyes. They showed the innervation to consist of a plexiform arrangement of delicate preterminal and terminal axons which were interwoven in different planes and ended as free axonal filaments. Free nerve endings were shown beneath the endothelium of Schlemm's canal and within the trabecular meshwork that forms the inner wall of Schlemm's canal. These workers directed attention to the possible role of nerve fibers and endings in the regulation of intraocular pressure.

Indeed the past decade has seen the reporting of many extraordinary studies on the trabecular meshwork and its role in normal and glaucomatous eyes. Rones has published a perceptive paper on "A mechanistic element in trabecular function." Zimmerman has demonstrated beautifully that hyaluronic acid occurs in the trabecular meshwork and speculates whether this substance influences the facility of aqueous outflow or whether its shock-absorbing and lubricating functions might be important in keeping open the pathways from the anterior chamber to the canal of Schlemm. Becker and his group in Saint Louis have reported fine work in this field, especially on the facility of outflow, carrying on the work brilliantly conceived and still painstakingly pursued by Grant of Boston. In Europe, Goldmann, Ashton and his co-workers, François, Unger and Rohen, to mention only a few of the many tireless workers in this field have con-

tributed much to our knowledge. It is with regret that their work cannot be discussed in detail but time permits me no more than cursory mention of any portion of the trabecular meshwork other than the canal of Schlemm and its outlets—the inner canals of Sondermann.

Part II

Just as the trabecular meshwork may be considered the most important of the four tissue layers of the limbus, so one might consider Schlemm's canal the most important part of the trabecular meshwork. Certainly it is the part about which the greatest controversy has raged.

In 1830 Schlemm drew attention to a canal existing in the human eye in almost the same region as the canal which Fontana had described in animals. Schlemm called the canal the sinus venosus.

Most textbooks picture the canal of Schlemm as an oval slit with no connection with other vessels. Study of serial sections shows the canal to be a plexiform, varicose structure.

The posterior surface of the canal of Schlemm is the trabecular meshwork. Its anterior surface is the sclera. The anterior surface of the canal gives rise to vessels which carry the aqueous from the canal to the anterior ciliary veins and through the ciliary body to the vorticose veins. These vessels are called external collector channels.

External collector channels

From 25 to 35 in number, the external collector channels arise around the entire circumference of the canal of Schlemm at irregular intervals. There may be from three to five within one mm. and then none for two mm. For each external collector channel there are about five inner canals of Sondermann.

The collector channels anastomose into a very complex deep intrascleral plexus before sending branches either to meet the anterior ciliary veins or to pass into the ciliary body. When a branch reaches the scleral surface, it is called an "aqueous vein."

Since the almost simultaneous, although independent, clinical findings of aqueous veins in normal and pathologic eyes by Ascher (1941) and Goldmann (1946) other workers have been stimulated to make detailed anatomic studies of these physiologic connections between the canal of Schlemm or the meshwork surrounding it and the episcleral plexus. Thomassen and Bakken, by injecting India ink into the anterior chambers of four eyes, found that aqueous veins originated from Schlemm's canal and histologically found no difference between aqueous and other veins.

Ashton, using Neoprene casts for his work, showed that two of the veins he studied were seen to arise directly from Schlemm's canal by a hook-shaped type of origin. Four other aqueous veins did not arise directly from Schlemm's canal but were connected to it by an anastomotic branch between the superficial and deep scleral plexus. All aqueous veins described by Ashton were of the striated or laminated variety. Ashton concluded that his findings confirmed Ascher's belief that the occasional branches between the superficial and deep scleral plexuses are the anatomic substrata of at least a great many of the aqueous veins.

Theobald constructed a model from serial sections, showing the origin of an aqueous vein from the canal of Schlemm. This vein zigzagged through the sclera to the scleral surface in an almost perpendicular manner. There is an extensive literature on this subject which Theobald brought up to date in 1955.

Although the outer wall of Schlemm's canal with its aqueous veins is anatomically well known, this knowledge is not valuable for its inner wall—the one separating the canal from the anterior chamber. Most theories about the outflow of the aqueous

humor through the scleral trabeculae toward the canal of Schlemm are based upon different hypotheses but none of them seems to be proved with certainty.

By far the most important problem in connection with the physiologic functions of Schlemm's canal is to determine the part it plays in the elimination of intraocular fluids, especially the aqueous. Ever since the discovery of the canal, a controversy has surrounded its role in the elimination of fluid from the anterior chamber and many investigators by injecting various substances into the anterior chambers of experimental animals have sought to prove or disprove the existence of open communications between the anterior chamber and the canal.

Schwalbe (1870), believing the canal to be a lymphatic vessel, although normally empty, by exerting gentle pressure succeeded in injecting the canal and anterior ciliary veins with dye solution introduced into the anterior chamber. In this way he affirmed the existence of these connections. In 1895 Leber stated that what Schwalbe and his followers considered an open communication was in reality an osmosis due to differences in pressure between the anterior chamber and the anterior ciliary veins. Later Schwalbe was inclined to adopt Leber's theory.

Sondermann in 1933 took an entirely different view. He asserted that in the angle of the anterior chamber the pressure is normally in equilibrium, and is modified only under the influence of systolic and diastolic variations. This change in pressure produces the phenomenon of filtration. Sondermann was of the opinion that Schlemm's canal contains aqueous humor, and that the pressure in it is less than that of the ciliary veins at the point of their departure from the sclera. The aqueous humor is drawn into Schlemm's canal by filtration and not by osmosis.

To solve the question of the elimination of the fluid of the anterior chamber, Sondermann injected red blood corpuscles into an ape's eye, and was convinced that the contents of the chamber passed into Schlemm's canal. Unlike India ink and similar fluids, blood has the advantage that it is not a foreign body and does not cause irritation and create unphysiologic conditions. Sondermann believed that Schlemm's canal with its inner and outer canals is the chief means of absorption, while only secondary importance could be ascribed to the iris.

The literature of the years intervening between the work of these early investigators and present-day studies is replete with reports of the results of various injection and perfusion experiments. To list all of them would take far more time than has been allotted to the delivery of this lecture. It seems pertinent, however, to mention more briefly than they deserve some of the more recent contributions to this field.

In 1955 François and his co-workers studied the anatomic relations of the inner wall of Schlemm's canal by microradiography, and they found that, after injection of Thorotrast or Angiopac into the anterior chamber of the eye, or directly into Schlemm's canal, and after study of the microradiographic patterns, that (1) a direct communication exists between the anterior chamber and Schlemm's canal and (2) on the level of the scleral trabeculae there is a system of clefts which empty by orifices into Schlemm's canal, and (3) the diameter of these orifices measures more than 1.5μ and less than 2,25μ.

Grant (1955) investigating the facility of flow through the trabecular meshwork attempted to evaluate the role of the corneoscleral meshwork as an anatomic factor in resistance to aqueous flow and concluded that the trabecular meshwork offers little resistance to aqueous outflow, but that the principal resistance is probably in the immediate outlets from Schlemm's canal.

Peter, Lyda and Krishna (1957), using the perfusion technique of Bárány, investigated the effect of uniform-sized latex particles on the resistance of the anterior

chamber angle in enucleated rabbit eyes. The particles were 0.13, 0.26, 0.36, and 0.88μ in diameter. They found no significant correlation between the diameter of the particle used and the change in resistance to flow. Adding hyaluronidase to the perfusate produced no change in resistance in latex-treated eyes. Intercameral perfusion of enucleated rabbit eyes with latex particles of less than one μ in diameter and their microscopic study revealed the particles to be found in the trabecular meshwork as well as in the scleral and episcleral vessels. It appeared that the greatest degree of resistance to latex perfusion occurs in the region of the inner wall of Schlemm's canal.

In his discussion of this paper, Ashton remarked that "it would appear that the degree of porosity of the meshwork is dependent not only upon the pore size but also upon the width of the intratrabecular spaces, which necessarily varies with the degree of compactness in the meshwork. . . . I wonder whether injection of Neoprene into the anterior chamber might not compress the meshwork to such a degree as to give an entirely false impression of its normal porosity."

In January, 1959, Karg, Garron and co-workers perfused 12 human eyes obtained from the eye-bank with graded latex microspheres of various sizes. Particles of 1.2μ and smaller in diameter passed through the eye without appreciable loss in concentration. There was some interference with the passage of 1.8μ and 3.0μ particles, as they emerged noticeably less concentrated than in the original perfusion fluid. Particles 5.6μ in diameter did not perfuse.

Sondermann (1933) was the first to describe definite communications between the canal and the trabeculae. He found that the inner canals, which now bear his name, are lined with endothelium. They branch off at right angles to the canal and then immediately run parallel to the course of the canal. The inner canals are narrower and usually more numerous than the external channels and they are in open connection with the fissures of the trabeculae.

If some think (Schwalbe, 1870) a direct communication exists by a system of trabecular clefts, others (Rochon Duvigneaud, 1893) agree with either an osmotic process for noncolloidal substances (Friedenwald, 1936), or a diffusion process, or a filtration process (Fortin, 1942), or an ultrafiltration process.

Theobald (1934) and Thomassen and Bakken (1951), among others, confirmed Sondermann's observation that there exists a direct communication.

In 1956 François, et al., after studying the influence of hyaluronidase on the permeability of the inner wall of Schlemm's canal concluded that, following use of this substance: (1) The trabecular clefts and their orifices at the level of the inner wall of Schlemm's canal are enlarged but only in a poor manner; (2) the permeability of the connective tissue building up to trabeculae has increased; (3) there is no evidence that new orifices are added to those already existing, but that the passage of the contrast fluid occurs in a more direct manner.

Flocks (1956), studying tangential sections, concluded that the endothelial-lined inner canals described by Sondermann as direct communications between the anterior chamber and Schlemm's canal were artefacts; in tangential sections no such structures were seen. Flocks is of the opinion that the openings in the canals as pictured by Sondermann and by Theobald are too large, since they measure 10μ to 25μ.

It is difficult, in my opinion, to evaluate tangential sections because all land marks are absent.

In 1958, Garron and co-workers, using 1.0 by 1.0 by 3.0-mm. specimens for electron microscopy appeared to confirm that small pieces of tissue may not give all the findings. They said that, since they had previously demonstrated by other means the openings which complete the pathway of the aqueous humor from the anterior chamber into the

canal of Schlemm, it was interesting that there was no evidence of such openings in the electron micrographs. They did not regard this as surprising, however, since the chance of finding one of these openings in a thin section is remote.

To illustrate this, Theobald (1934) constructed a diagram from 810 serial sections. This diagram shows that the external collector channels are distributed in a very uneven manner about the entire circumference of the canal of Schlemm system. There are areas where the collector channels are more than two mm. apart, and several areas where there are as many as four collector channels in one mm. When choosing biopsies at random, one may not be fortunate enough to choose the mm. with four collector channels but may choose the two mm. in which there is no vascular drama. In this particular eye there were 29 external collector channels. The passages we call the inner canals of Sondermann number about five to each collector channel. The inner canals of Sondermann do not pass like tubules through the depths of the meshwork. The name (Sondermann's canals) is applicable to the break in the outermost layers of the trabeculae where these minute channels immediately become a part of the intratrabecular spaces, which many authors liken to the pores of a sponge. In describing these openings, Sondermann wrote "they leave the canal at right angles and immediately become parallel to it." His illustration was diagrammatic, picturing the pathway from the anterior chamber to the canal.

Ashton in his 1956 study reported that "numerous sections were seen in which a pore in the inner wall of Schlemm's canal opened freely into an intratrabecular space. Furthermore, in other cases, a few red cells were seen lying within the canal in a random fashion, while adjacent to them, in the nearest intratrabecular space, were seen other red cells, so oriented as to suggest that they were in fact trapped between two laminae of the meshwork. This appearance was seen in eyes in which no blood was present in the anterior chamber, and it therefore seems clear that the red cells must have gained access to the intratrabecular spaces from the canal of Schlemm. Serial sections of a normal post-mortem eye confirmed the impression of the existence of channels leading from the canal of Schlemm into the intratrabecular spaces."

In August of this year, Unger and Rohen continued their work on the trabecular meshwork in a paper on "Studies on the histology of the inner wall of the canal of Schlemm." Fourteen eyes enucleated because of tumors or perforating injuries were studied with regard to the normal structure of the meshwork, especially the inner wall of Schlemm's canal by means of tangential sections. In the "pore tissue" of Flocks of the outermost part of the trabecular meshwork there were endothelial-lined tubes which are probably identical with the internal canals according to Sondermann, as yet described only in cross section, and they often observed Sondermann's internal canals in series of sections of the trabecular meshwork and, therefore, held them to be permanent structures. They believe that "these passages are not merely pores, but rather pathways which tend to establish in the mazelike spaces of the meshwork the shortest possible connection between the chamber and the canal via a strip of openings."

Figures 1, 2, 4, 5, 6, and 7 illustrate findings on the canal of Schlemm and Sondermann's canals which have been confirmed by various authors.

Part III

All of these discussions and controversies, experiments, studies and investigations of the limbal area and particularly of the trabecular meshwork and the canal of Schlemm have one common purpose and that is, of course, to correlate the anatomic structure and physiologic functions of this area with the pathogenesis of glaucoma, as well as other diseases of the eye.

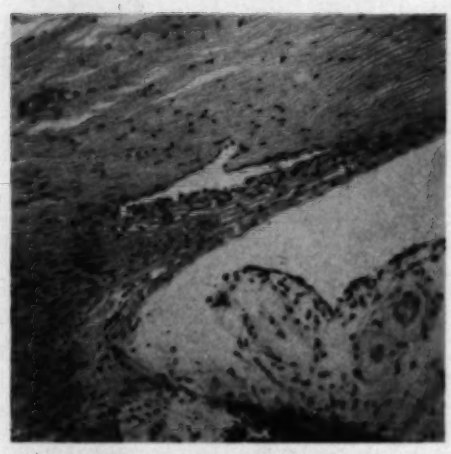

Fig. 1 (Theobald). Photomicrograph of normal eye, showing absence of blood in the anterior chamber.

Vogt in his *Atlas of Slitlamp Microscopy* (1921) was among the first authors using modern techniques to describe diseases of the limbal area. Among other things he tells us about the gerontoxon which is adjacent to the limbus and about the role the limbal vessels play in inflammations of the cornea and in iridocyclitis. In advancing age, Vogt notes senile changes occurring in the limbus; there may be pigment and/or calcium deposits. The pigment extends into the clear interval of the cornea, as well as the gerontoxon.

In the literature of the years since Vogt there are hundreds of references to the role of the limbal area in the diseased eye. Regrettably much of this work cannot now be mentioned. However, these many authors have contributed the groundwork for much of the research of the last five years.

In 1955, Teng, Paton and Katzin reported on the primary degeneration in the vicinity of the chamber angle as an etiologic factor in wide-angle glaucoma. Microscopic study of from three to 20 slides from each of 2,792 eyes revealed a type of degeneration in many so-called normal eyes which these authors could not find previously reported. The incidence of the change was fairly high after the age of 40 years. The location of the degeneration was in the drainage area and was most often found in the external portion of the trabecular meshwork where the fibers were usually thinner and more compactly arranged.

Although Teng and co-workers demonstrated degeneration of collagen and elastic fibers, they were unable to describe the nature of the degeneration. These same authors were able to study serial sections from the eyes of three patients with early wide-angle glaucoma and found them to exhibit the same type of degeneration in more extensive and advanced forms. Early in 1957, these same authors reported on the fourth case of this type.

The changes Teng and his associates observed were proliferation of the endothelium and a strong tendency toward adhesion between the trabecular spaces, the walls of Schlemm's canal, and the walls of the collector channels. By these processes many passages were obliterated. There were signs of recanalization in the collector channels but it did not seem extensive enough to reestablish outflow.

Fig. 3 (Theobald). The inner canals as described by Sondermann leave the canal of Schlemm at right angles, immediately becoming parallel to it.

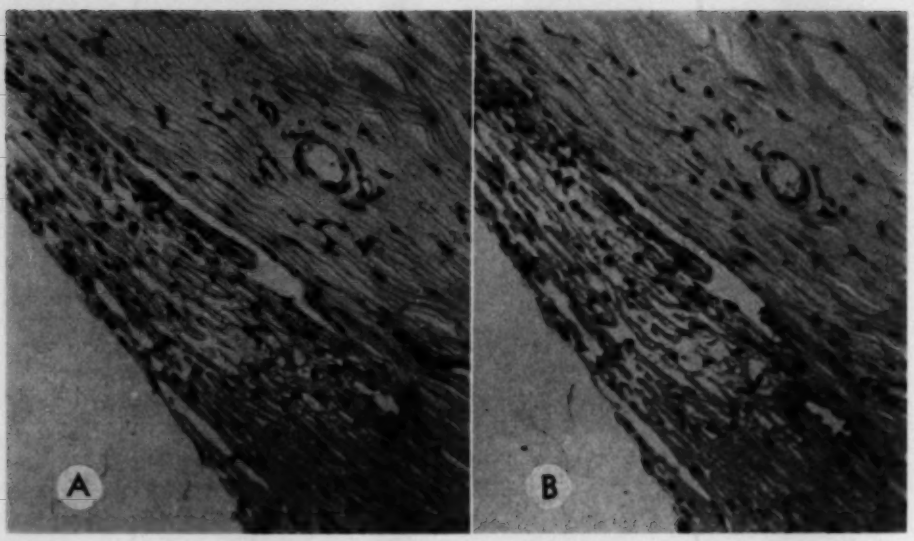

Fig. 4 (Theobald). A and B are adjacent sections from the same eye and show a Sondermann's canal entering Schlemm's canal at the center.

Theobald and Kirk (1956) reported thickening and sclerosis of the trabeculae and compression of the collector channels in the sclera in their study of eyes with primary open-angle glaucoma. They noted narrowing of Schlemm's canal and a spongy edema of the external trabeculae, with pigment deposits in this area. They concluded that hypertrophy and sclerosis of collagenous fibers of the sclera, associated with aging, compresses and narrows intrascleral veins, producing glaucoma (fig. 8).

In 1958, Flocks, in reporting his study on the pathology of the trabecular meshwork in primary open-angle glaucoma, confirmed the findings of Teng, Paton and Katzin, but noted that thickness of the trabecular beam and sclerosis of the trabeculae, as reported by Theobald and Kirk, were not invariably present. As the result of his study, Flocks

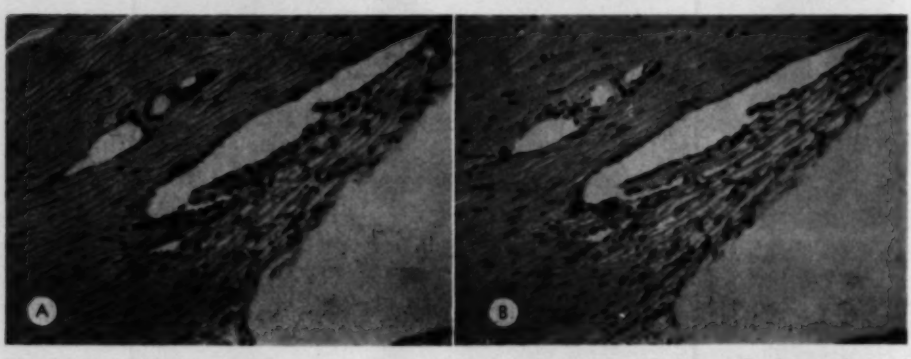

Fig. 5 (Theobald). A and B are adjacent sections from the same eye and show a Sondermann's canal entering Schlemm's canal at the posterior end.

Fig. 6 (Theobald). Photomicrograph, showing inner canal entering canal of Schlemm and an external channel on its anterior surface.

proposed a new theory for the pathogenesis of primary open-angle glaucoma in which he suggested that persons destined to have this disease possessed relatively vulnerable trabeculae which could be injured by levels of intraocular pressure that ordinarily would not damage the trabeculae or optic nerve. When the curve of intraocular pressure, which normally slowly rises with advancing age, reaches the point where enough trabecular degeneration has occurred to cause insufficiency of the pressure-regulating mechanism, progressive glaucoma is instituted. In Flocks' opinion, changes in the trabecular meshwork are secondary to the elevated pressure which is probably secondary to failure of the pressure-regulating mechanism.

In September, 1958, Kornzweig, Feldstein and Schneider reported on the pathology of the angle of the anterior chamber in primary glaucoma. They were able to obtain eyes which had been affected by simple glaucoma and acute episodes of congestive glaucoma, without surgical intervention. They had 11 such eyes from seven patients. The trabeculae of all their sections showed varying degrees of thickening and sclerosis, with corresponding narrowing and obliteration of the intratrabecular spaces. Pigment granules and cells were present to some extent in all eyes and were scattered throughout the trabeculae. Schlemm's canal showed varying degrees of patency, from normal to almost complete occlusion. When it was occluded,

Fig. 7 (Theobald). Sondermann's canal enters canal of Schlemm at center and external channel leaving at center.

the cause seemed to be endothelial proliferation or compression by thickened or degenerated trabeculae. All of these factors, by narrowing or occluding the outflow channels for the aqueous from the anterior chamber, may help to raise the intraocular pressure.

In 1958, Unger and Rohen, in a paper previously mentioned in this lecture, reporting on the pathologic reactions in the trabecular meshwork said that the equatorial elastic reticulum, which represents the mechanical basis of the trabeculae, changes very little in case of disease, while the endothelium and the "glass" membrane connected with it show characteristic reactions. The "glass membrane, comparable to a basement membrane shows an increase of substance in various cases of glaucoma, as well as in globes enucleated because of tumors or perforating injuries. In eyes with absolute glaucoma this process reaches extreme degrees, so that, in this way, too, the angle becomes obliterated. The increased resistance to outflow might thus be explained morphologically."

In a recent study soon to be published, Unger and Rohen continue their investigation of the trabecular meshwork on biopsy material obtained in 50 cases of simple glaucoma by Elliot trephination. Histologic examination of this material permitted the authors to observe two types of alteration (1) changes in the "glass" membrane of the trabecular meshwork, with or without intratrabecular adhesions and (2) changes in the inner wall of Schlemm's canal with or without circumscript proliferation of endothelial or retothelial cells. Four cases showed an excessive, tumorlike increase in the number of cells and, in one case, the meshwork was replaced by amorphous tissues. The authors conclude that these alterations are degenerative in nature and that they contribute to the obliteration of the intratrabecular aqueous passages.

Garron and others in an electron microscopic study of ocular tissue concluded that it is probable that the trabecular meshwork, in the portion adjacent to Schlemm's canal, is the site of changes responsible for open-angle glaucoma. The inner wall of the canal is lined with endothelial cells, many of which appear to have giant cytoplasmic vacuoles. The adjacent meshwork is composed of trabecular bands, loosely arranged to form intercommunicating spaces.

I have mentioned here only the studies with which I am most familiar. There have been many, many others, each one contributing in some measure to a minute understanding of the pathologic changes taking place in the limbal area of an eye suffering from any one of the glaucomas. The literature is so voluminous that to summarize all of it is impossible but, from the numerous studies, certain rather clear-cut conclusions seem to emerge:

1. In primary open-angle glaucoma there is obstruction in the channels leading to and from the canal of Schlemm.

2. This obstruction may be due to (a) degeneration of collagen tissue and proliferation of endothelium of Schlemm's canal, (b) thickening and sclerosis of the trabeculae, (c) deposition of pigment granules, (d) tumorlike increases in the endothelial and wandering cells, and (e) replacement of the meshwork with amorphous tissues, (f) compression of the collector channels in the sclera.

The picture in simple glaucoma is not clear. However, as Duke-Elder pointed out in his Bowman Lecture (1957), the fact remains that the trabeculae have been found normal in relatively few cases of early simple glaucoma which have come to histologic examination.

Maumenee's contribution to the pathogenesis of congenital glaucoma is his suggestion that the raised intraocular pressure in these cases is due to an abnormal insertion of the longitudinal and circular bundles of the ciliary muscle into the trabecular fibers. This defective insertion tends to compress the scleral spur forward and externally, thus narrowing Schlemm's canal.

Secondary glaucoma may be due to any of a number of disease mechanisms reacting on the trabecular area. To summarize briefly:

1. Hypopyon and inflammatory cells and granules of pigment liberated by the injury or disease process may block off intratrabecular spaces and so block the exit of the aqueous.

2. Edema of the iris and ciliary body may push the iris root against the trabeculae.

3. Agglutination or organization of connective tissue may form a permanent synechia.

4. Posterior synechias which cause the iris to attach itself to the anterior lens capsule.

5. Contusions cause a rise in tension by producing edema of the intraocular tissues and hemorrhages.

6. Exfoliation of lens capsule.

7. Intraocular tumors.

Conclusion

God has made all things and man is just beginning to discover what has been here all the time. For over a hundred years workers in our specialty have been groping toward an understanding of what really takes place in the limbal area of the human eye. That our knowledge is still incomplete is attested by the controversies still surrounding the physiology of this area, particularly of the trabecular meshwork and the canal of Schlemm.

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GLAUCOMA FAMILY STUDY*

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While hereditary glaucoma had been reported as early as 1842,[1] no study of relatives of glaucoma patients for the purposes of detection and study of the preclinical stages was undertaken before 1951. Since 1951, two reports of such studies demonstrate a high incidence of glaucoma in these relatives.[2,3] The present study was undertaken to evaluate pressure, facility of outflow, discs, and visual fields in the close relatives of patients with established glaucoma, in the hope that such a population, with a comparatively high probability of developing glaucoma, might demonstrate the earliest detectable abnormalities in the pathogenesis of the disease process.

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Procedure and Background

In reviewing the literature on glaucoma—in particular, chronic simple glaucoma—several points of particular importance could be established.

1. Heredity definitely plays a role in the pathogenesis of at least some cases of glaucoma. From 13 to 25-percent of glaucoma patients have a family history of glaucoma.[2-6] In a disease with the over-all incidence of glaucoma, the chances of this occurring on a nonhereditary basis are negligible.

2. While glaucoma apparently can be transmitted as a recessive characteristic,[2,5] in most pedigrees it demonstrates the pattern of dominant hereditary.[4,7,8]

3. In the pedigrees which have been examined, the penetrance of glaucoma is about 74 to 80 percent (that is, some three fourths of people capable of transmitting glaucoma to succeeding generations demonstrate the hereditary character).[4]

From the above, two plans of study might be proposed. First, one could follow a group of close relatives of people with familial chronic simple glaucoma (at least two cases in the family) from infancy to old age. Approximately 35 to 40 percent of these relatives would be expected to develop glaucoma and might demonstrate abnormalities preceding the actual disease. A second approach would be to study the close relatives of all ages. If glaucoma is an end-result of some inherited tendency or abnormality, such a study might reveal its occurrence and progression to the actual disease entity. Since the second plan appeared to be more feasible, a study of relatives of glaucoma patients was undertaken.

Criteria for Study

In the present study, families were selected in which there were at least two known cases of chronic simple glaucoma. No attempt was made to study the initial patients with glaucoma, although in most cases the tonographic records with brief descriptions of the clinical status of the patients were available and were checked.

The people studied were all siblings, children, and parents of glaucoma patients, and all were above the age of 15 years. The age of 15 years was arbitrarily selected as an age at which good co-operation of the patient could be expected in the performance of the test procedures.

For each family a "family tree" was prepared by contacting and interviewing a member of the family. The members of the family who lived near St. Louis and who fitted the above criteria were then contacted and asked to come to McMillan Hospital for an eye examination and glaucoma work-up without charge. If an ophthalmologist was caring for the patient, he was contacted and the program was explained to him. Permission of the ophthalmologist to see the patient was requested and in no case was refused.

It was suggested to members of the families that relatives living outside of the St. Louis area be contacted and be seen by an ophthalmologist for an eye examination. This suggestion resulted in finding at least one case of glaucoma in a relative living in Florida. Also, several relatives were seen who did not quite fit the established criteria. These were more distantly related people who, for example, had a parent who was a sibling of a glaucoma patient, but the parent died at an early age (and therefore, perhaps, didn't have time to develop glaucoma). The findings from this group have been kept separate from those of the group which met the preset criteria.

When a relative was seen, he was first given a brief discussion of glaucoma and why it was suggested that he have an examination. In many instances the people seen had a parent or sibling blind from glaucoma and were most anxious to be examined.

After the above discussion, the examination was carried out in the following order:

1. Visual acuity—with and without glasses.

2. External examination, motility, and pupillary reactions.

3. Slitlamp examination.

4. Visual field examination. Peripheral fields were tested with a Curry and Paxton projection perimeter, using a 3.0-mm. white projected test object at a distance of 330 cm. Central fields were measured using a tangent screen at one meter and white circular test objects inserted into a black wand. For measurement of the blindspot, the smallest test object which encompassed the blindspot was used.

5. Ophthalmoscopy.

6. Applanation tonometry, tonography, and water provocative test. All patients were asked to fast for at least four hours prior to the examination. All tonograms were done at the Washington University Tonography Laboratory, using a Mueller electronic tonometer and a Leeds and Northrup recorder. In each case, applanation tonometry was performed, followed in a few minutes by the first tonogram. Following the tonogram, the patient was given one liter of water and asked to drink it within five minutes. This was possible in about 95 percent of the cases. Following the consumption of the water, the patient was asked to wait for 40 minutes, at the end of which time the applanation tonometry followed by tonography was again performed. Scleral rigidity was determined by comparing the applanation readings with the Schiøtz measurements (taken from the electronic tonometer), using the Friedenwald nomogram.[9]

7. Gonioscopy. Gonioscopy was done with a Zeiss four-mirrored gonioprism in the sitting position at the slitlamp. The angles were graded using the Shaffer classification.[10]

The above examinations, including tonography, required about two and one-half hours. Following the examination, the findings were explained to the patients. If the findings were classified as "abnormal" (see criteria below), the patients were referred to their ophthalmologists for further study and treatment. If they had no ophthalmologist, a list of qualified specialists was provided for the patient's choice. If the findings were "suspect" this was also explained, and the patient was asked to return at another time (usually four to six months) for repeat tests. If the findings were "normal," it was explained that at the present time there was no evidence of glaucoma, but that there was no assurance that the findings would always be normal and that periodic testing should be done. In all cases, copies of the findings were mailed to the patient's ophthalmologist with a letter thanking him for permitting his patient to be seen.

Definition and criteria for diagnosis

As mentioned earlier, the purpose of the study was to detect abnormalities which precede or are an early part of the entity called glaucoma. For this reason, it was necessary to set arbitrary values for all of the tests and define them as "normal," "suspect," or "abnormal" without stating a necessary relationship of these values to glaucoma. In setting values for the tests, wherever possible, the distribution of the results of such tests in the normal population, as determined in previous studies, was considered.[11-13] Values equal to or less than two standard deviations from the normal mean were considered "normal," values between two and three standard deviations from the mean were considered "suspect," and values more than three standard deviations from the mean were considered "abnormal." This method was used in setting limits for intraocular pressure, outflow facility, and increase of pressure after water. For some tests, for example, visual fields, the above procedure could not be used. For these tests, arbitrary limits were set. The values used for classification of results are shown in Table 1.

It has been shown that in the normal population the rise in intraocular pressure with water is only about 1.0 mm. Hg and that the change in outflow facility is negligible.[13, 14] For this reason, the same values for Po and

TABLE 1

VALUES USED FOR CLASSIFICATION OF TEST RESULTS

Procedure or Test	Normal	Suspect	Abnormal
Pressure (Po) (Schiøtz or Applanation)	<22 mm. Hg	22–24 mm. Hg	>24 mm. Hg
Outflow facility	>0.18	0.18–0.13	<0.13
Po/C	<100	100–200	>200
Increase in Po with water	<7 mm. Hg	7–9 mm. Hg	>9 mm. Hg
Gonioscopy	Grade 3 or 4	Grade 2	Grade 1 to closed
Discs	Small physiological or no cupping	Slight to moderate cup with or without nasal displacement of vessels	Moderate to severe cupping with pallor and nasal displacement of vessels
Visual field	No enlargement of the blindspot in one direction of >15° as measured from the fixation point	Enlargement of the blindspot of 15°–30°	Enlargement of the blind spot of >30°

C in the normal population can be used before and after water without the introduction of significant error.

The values for visual field examination are demonstrated in Figure 1. The values 15 and 30 degrees are measured from the center point of the chart. In order to be classified as suspect, the blindspot must be enlarged 15 degrees in one direction. Also, to be classified as abnormal, it must be enlarged 30 degrees in one direction—that is, enlargement 15 degrees above and 15 degrees below is still considered "suspect," rather than "abnormal."

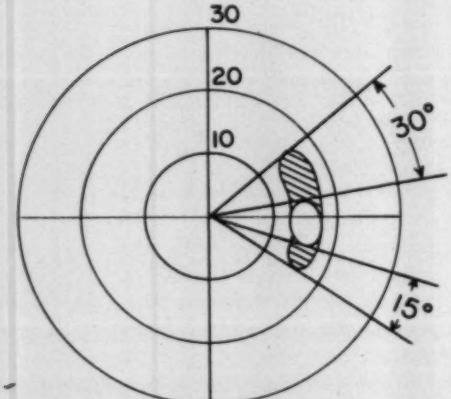

Fig. 1 (Becker, Kolker and Roth). Representation of a visual field chart, demonstrating enlargement of the blindspot of 15 and 30 degrees in one direction, as measured from the fixation point.

From the practical point of view, it became necessary to set some criteria for recommending treatment. For purposes of this study, treatment was recommended arbitrarily for any eye with a pressure of > 30 mm. Hg, either before or after water, either by Schiøtz or applanation, either with or without field loss.

RESULTS

Between November, 1958, and August, 1959, 110 siblings, children and parents of known glaucoma patients were studied in the manner previously described. These people

TABLE 2

AGE DISTRIBUTION OF GLAUCOMA FAMILY STUDY GROUP

Age (yr.)	Number	Percent
15–19	13	11.8
20–29	20	18.2
30–39	15	13.6
40–49	30	27.3
50–59	20	18.2
60–80	12	10.9

were from 24 unrelated families, in each of which there were two or more known cases of glaucoma. The age distribution of the study group is shown in Table 2.

In the entire group of 110 patients, six met the pressure criterion for recommending treatment. These six cases are individually described.

Case descriptions

Number IX–5

A 48-year-old white woman was referred by a private ophthalmologist because of a strong family history of glaucoma (father, several aunts and uncle, grandfather). No visual complaints or symptoms.

Examination. Visual acuity 20/20+ O.U. (corrected), discs normal, visual fields normal, open angles by gonioscopy.

Tonography.

O.D. Po 32 C = 0.03
O.S. Po 38 C = 0.05

Water provocative test done three months after previous test:

Before water	O.D.	Po	29	C = 0.08
	O.S.	Po	30	C = 0.06
After water	O.D.	Po	26	C = 0.08
	O.S.	Po	34	C = 0.03

Applanation.

Before water	O.D.	29
	O.S.	32
After water	O.D.	28
	O.S.	31

Impression. Chronic simple glaucoma.

Number VI–4

A 48-year-old white man was seen because of family history of glaucoma (brother and cousin). No visual difficulty except for early presbyopia.

Examination. Visual acuity 20/25 O.U. visual fields (peripheral and central) normal O.U., normal appearing optic discs without cupping, wide open angles (grade IV) by gonioscopy.

Tonography.

Before water	O.D.	Po	29	C = 0.08
	O.S.	Po	23	C = 0.07
After water	O.D.	Po	36	C = 0.06
	O.S.	Po	24	C = 0.11

Applanation.

Before water	O.D.	28
	O.S.	23
After water	O.D.	41
	O.S.	30

Impression. Chronic simple glaucoma.

Number IV–1

A 78-year-old white woman with a strong family history of glaucoma was referred by an ophthalmologist to be seen as part of the Family Glaucoma Study. She was known to have had cataracts for about three years and had noted some recent gradual decrease in vision.

Examination. Visual acuity 20/40 (corrected) O.U., open angles (grade III) on gonioscopy; visual fields, concentric constriction of field to 15 degrees O.D., definite Bjerrum scotoma with breakthrough to the periphery O.S., cupping of optic discs O.U.

Tonography.

O.D. Po 37 C = 0.08
O.S. Po 29 C = 0.06

Impression. Chronic simple glaucoma.

Number XXI–1

A 70-year-old white woman was asked to come in for an examination because of family history of glaucoma (father, brother, and aunt). She had no visual complaints at time of examination.

Examination. Visual acuity (corrected) 20/20 O.U., visual fields, Bjerrum scotoma with breakthrough to the periphery O.D., elongation of blindspot O.S., open angles (grade IV) by gonioscopy, definite glaucomatous cupping O.U.

Tonography.

Before water	O.D.	Po	42	C = 0.10
	O.S.	Po	33	C = 0.08
After water	O.D.	Po	49	C = 0.08
	O.S.	Po	32	C = 0.08

Applanation.

Before water	O.D.	39
	O.S.	30
After water	O.D.	44
	O.S.	36

Impression. Chronic simple glaucoma.

Number I–2

A 68-year-old white woman who was seen following the discovery of glaucoma in her daughter. No visual complaints, both eyes had always been good as far as she knew.

Examination. Visual acuity (corrected), O.D. 20/20; S.S. 20/40, deep glaucomatous cupping O.U., marked enlargement of blindspots O.U., open angles (grade III) by gonioscopy.

Tonography.

O.D. Po 47 C = 0.06
O.S. Po 40 C = 0.09

Applanation.

O.D. 46 O.S. 40

Impression. Chronic simple glaucoma.

Number XXIII–1

A 57-year-old white man was referred by an ophthalmologist because of strong family history of glaucoma. The patient had requested check and had no visual difficulties.

Examination. Visual acuity, O.D. 20/30; O.S. 20/25; visual fields (peripheral and central) normal O.U., open angles (grade III), broad central

TABLE 3

RESULTS OF TEST PROCEDURES IN 110 GLAUCOMA RELATIVES*

Test	Normal	Suspect	Abnormal	
Fields	206 (94.5%)	5	7	(a)
Gonioscopy	220 (100%)	0	0	
Discs	205 (93.2%)	10	5	
Po before water	188 (85.5%)	15	17	
C before water	164 (74.9%)	31	24	(b)
Po/C before water	165 (75.3%)	32	22	(b)
Po after water	184 (85.2%)	19	13	
C after water	128 (59.5%)	64	23	(b)
Po/C after water	129 (60.0%)	71	15	(b)
Increased in Po with water	211 (97.7%)	5	0	
Applanation before water	192 (88.8%)	14	10	(c)
Applanation after water	169 (78.2%)	32	15	
Increase in applanation with water	208 (97.2%)	5	1	(c)

* Recorded as number of eyes.
(a) Fields unreliable in one patient because of congenital nystagmus.
(b) One tonogram unsatisfactory for calculation of C or Po/C.
(c) Applanation readings not done on one patient before water.

cupping of the optic discs O.U. which extended almost to the temporal border.

Tonography.

Before water	O.D.	Po	33	C = 0.07
	O.S.	Po	25	C = 0.07
After water	O.D.	Po	37	C = 0.12
	O.S.	Po	20	C = 0.13

Applanation.

Before water	O.D.	33
	O.S.	26
After water	O.D.	40
	O.S.	24

Impression. Chronic simple glaucoma.

The findings in the total group of 110 patients (220 eyes) are summarized in Table 3, using the criteria already described. Two of the six patients individually described above did not have a water provocative test because the tonograms before water were considered diagnostic. For this reason, there are four less eyes in the "after water" tests than the number in the "before water" tests.

DISCUSSION

Before analyzing and discussing the results, an effort will be made to review some of the characteristics which glaucomatous eyes demonstrate in comparison with normal eyes.

1. Glaucoma may be characterized as an increase in intraocular pressure to levels which are pathologic. The difficulties with this definition arise from the statistical distribution of intraocular pressures and the overlap of normal and glaucoma. Secondly, pressures which are pathologic and lead to extensive damage and field loss in one eye may be tolerated for years without damage by another eye. The problem is usually resolved on the basis of clinical experience, deciding which pressures will eventually lead to damage.

2. A second characteristic of glaucomatous eyes is loss of visual field, accompanied by cupping of the optic discs. This field loss occurs in a typical fashion, resulting in a nerve-fiber bundle defect. For purposes of this study, we have defined an abnormal field as a typical defect of 30 degrees or more. A definition of glaucoma in terms of visual field loss, in the absence of causes other than elevated intraocular pressure, is probably the only one that can be universally accepted at the present time.

3. Aside from the above characteristics, glaucomatous eyes also show an impairment of outflow facility, as measured by tonography, and react differently than normal eyes to the water drinking provocative test.[11,14-16] Leydhecker found that 29 percent of glaucomatous eyes had a rise of 8.0 mm. Hg or more following the consumption of one liter of water, while normal eyes demonstrated a rise of about 1.0 mm. Hg.[13] Becker

and Christensen reported that the rise in pressure was also accompanied by a reduction in outflow facility in glaucomatous eyes, while in normal eyes the outflow facility did not change.[14]

Thus, the glaucomatous eye is one with an "elevated" intraocular pressure, an "impaired" outflow facility, characteristic field loss not explained by other causes, cupping of the optic disc, and a reaction to the water drinking provocative test consisting of a rise in pressure and further decrease in outflow facility. The nonglaucomatous eye is one with a "normal" intraocular pressure and outflow facility, no field loss or cupping (other than physiologic), and no significant changes in pressure or outflow facility following the water drinking test.

Visual fields

Besides three abnormal fields in the group of six patients with pressures over 30 mm. Hg, there were four other abnormal and two suspicious visual fields. Of the abnormal fields, one was in a 38-year-old white man who has peripapillary chorioretinal atrophy which is believed sufficient to explain the defect. Another was in a 58-year-old white woman with occlusion of a branch of the central retinal artery. The other two were bilateral Bjerrum scotomas in a 53-year-old white woman, confirmed on repeat examination, who had a perfectly normal water provocative test, no cupping, and no other fundus abnormalities to explain the loss. The patient is to return soon for repeat evaluation and possible skull X-ray films and neurologic examination. One of the two suspicious fields was that of the opposite eye of the man above with the chorioretinal atrophy. The other was an enlarged blindspot in a 46-year-old white man with no other abnormalities.

Discs

Besides the cupping of the discs in four of the six patients with pressures over 30 mm. Hg, there were seven optic discs which were believed to be suspicious of glaucomatous cupping. These were the eyes of four individuals, two of whom had suspicious to abnormal findings of pressure and outflow facility, but normal visual fields. Another had suspicious discs, but essentially normal findings on all other tests. The other person had a definite difference in the appearance of her optic discs, one being suspicious and the other having normal appearing physiologic cupping. The pressures in both eyes by applanation were suspicious after water (23 mm. Hg). Visual fields were normal.

Gonioscopy

All of the patients seen were found to have angles which were considered incapable of occlusion—that is, grade 3 or 4, by Shaffer classification. This is largely accounted for by the methods of selection of families for the study.

Intraocular pressure

For the entire family population, the average intraocular pressure before water was 18.0 ± 5.2 mm. Hg and essentially unchanged after water (17.9 ± 4.8 mm. Hg). Both of these values are significantly higher than the average normal pressure of 16.1 $\pm$ 2.8 mm. Hg ($t = 5$).[11]

As noted previously, the sole criterion used for the recommendation of starting therapy for glaucoma was an intraocular pressure of >30 mm. Hg, which occurred in six individuals. While, perhaps, not everyone will agree that this pressure constitutes glaucoma, it was felt that the chances of it being pathologic (three had abnormal fields) were great enough to warrant therapy. These six represent a prevalence of 5.5 percent. However, if only the 62 people above the age of 40 years are considered, the prevalence is 9.7 percent or about five times the usual reported incidence in the general population over the age of 40 years. In addition, there were five other people (seven eyes) who had an intraocular pressure of greater than 24 mm. Hg after water, as measured by

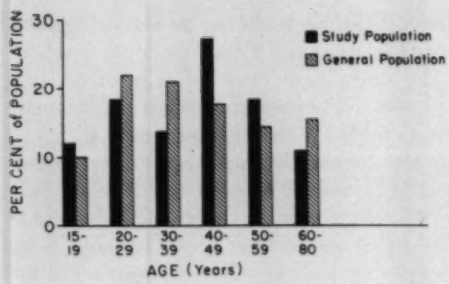

Fig. 2 (Becker, Kolker and Roth). Comparison of the age distribution in the study group of 110 relatives of glaucoma patients and the general population, ages 15 to 80 years.

Schiøtz tonometry. Four of these were more than 40 years of age. Together, these 10 people constitute a prevalence of elevated pressure to this degree of abnormality of 16.1 percent in the family population above the age of 40 years.

While these results are impressive, they become even more so when the population is corrected for age distribution. In Figure 2, the age distribution of the family study group is compared with that of the general population between the ages of 15 years and 80 years.[17] In the population 40 years of age and older, it can be seen that the family study group contains a larger percentage in the 40 to 49-year age group than in the general population. Since the incidence of glaucoma is known to rise steeply in the older age groups, the prevalence in the present study would probably be higher if the percentage of older people were the same as in the general population. That this is very likely the case is indicated by the fact that an intraocular pressure of >30 mm. Hg was found in 25 percent of those 60 years of age and older. Correcting for age distribution, the prevalence of a pressure >30 mm. Hg would

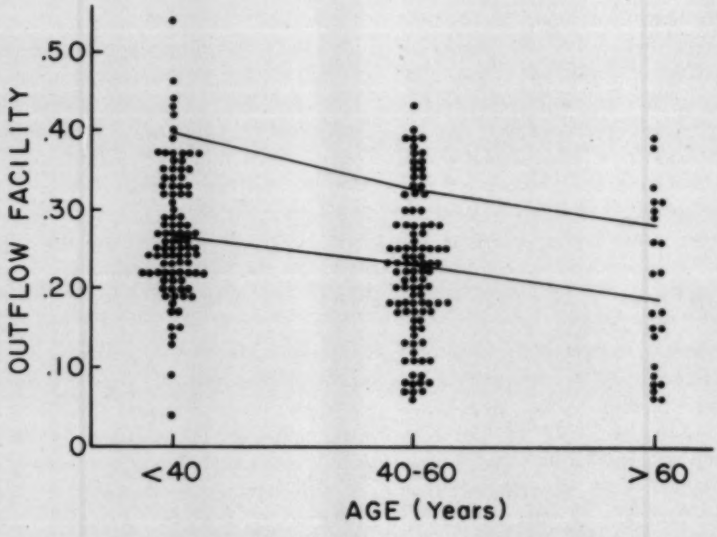

Fig. 3 (Becker, Kolker and Roth). Facility of outflow before water in 219 eyes of 110 relatives of glaucoma patients compared with the average facility of outflow (± one standard deviation) at various ages for a normal population (909 eyes).

be 12.1 percent in those above the age of 40 years. Likewise, the prevalence of a pressure >24mm. Hg would be 17.3 percent for this age group.

It has been shown that in many people the consumption of a large quantity of water results in a decrease in scleral rigidity, so that pressures are underestimated when measured by Schiøtz tonometry.[18] The response of the patients in this study supports this finding. Before water, 85.5 percent of the eyes had a normal intraocular pressure (within two standard deviations of the normal mean) as measured by Schiøtz tonometry. The percentage as measured by applanation was 88.8 percent. After water, the percentage of normal pressure by Schiøtz was 85.2 percent, or essentially unchanged. As measured by applanation tonometry, however, only 78.2 percent had a normal pressure. Thus, 21.8 percent of the total family population had an intraocular pressure of 22 mm. Hg. or above after water.

Outflow facility

The values of outflow facility for the study group are plotted in Figure 3 (before water) and Figure 4 (after water). The lines represent the mean ± one standard deviation for a normal population. As will be noted, a considerable number of the glaucoma relatives fall below the standard deviation line.

The value for outflow facility for the entire group was 0.242 ± 0.091 before water and 0.224 ± 0.091 after water. Both of these are significantly lower than the values in the normal population of 0.276 ± 0.047 ($t = 5$ before water, $t = 8$ after water).[11] Expressed in another way, only 74.9 percent

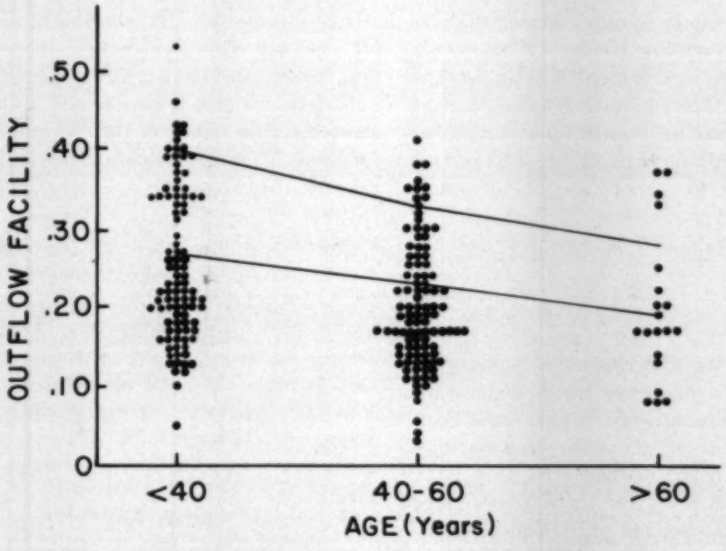

Fig. 4 (Becker, Kolker and Roth). Facility of outflow 40 minutes after the consumption of one liter of water in 215 eyes of 108 relatives of glaucoma patients compared with the average facility of outflow (± one standard deviation) at various ages for a normal population (909 eyes).

TABLE 4

RESULTS OF TEST PROCEDURES IN "DISTANT" GLAUCOMA RELATIVES*

Test	Normal	Suspect	Abnormal		
Visual field	40 (97.6%)	1	0	(a)	(a′)
Gonioscopy	43 (100%)	0	0		
Discs	43 (100%)	0	0		
Po before water	41 (100%)	0	0	(b)	
C before water	34 (82.9%)	6	1		
Po/C before water	37 (90.2%)	4	0		
Po after water	41 (95.3%)	1	1		
C after water	31 (72.1%)	8	4		
Po/C after water	36 (83.7%)	4	3		
Increase in Po with water	41 (100%)	0	0		
Applanation before water	40 (93.0%)	3	0		
Applanation after water	38 (88.4%)	4	1		
Increase in applanation with water	43 (100%)	0	0		

* Recorded as number of eyes.
(a) In one person visual fields were unreliable.
(a′)One person had a perforating injury to one eye as a child. Because of this, none of the findings in this eye are included.
(b) In one person, the tonogram before water was completely unreliable. All findings involving this tonogram have been excluded.

(164/219) had a normal outflow before water. After water, this dropped to 59.5 percent (128/215). Thus, a large number of eyes in the family group reacted to water with a fall in outflow facility. Of the people in the study, 16.4 percent had an outflow facility of <0.13 (more than three standard deviations from the normal mean) in one or both eyes. This corresponded to 22.5 percent of those over 40 years of age who presented this degree of impairment. The age corrected prevalence was 25.5 percent for this age group.

Po/C

Recalling the characteristics of the glaucomatous eye, one term which defines and describes these findings is the ratio Po/C after water. In one series 97 percent of eyes with proven glaucoma had a Po/C $\geq$ 100.[14] In the present study, the Po/C $\geq$ 100 group comprised 40.0 percent of the entire population studied. It is of interest that this is the anticipated finding for a characteristic transmitted by dominant inheritance with an 80 percent penetrance. It is obvious that it will be necessary to follow the study population over a period of years in order to determine which patients develop glaucoma, and if a ratio Po/C $\geq$ 100 after water has predictive value for subsequent glaucoma.

In addition to the main group of glaucoma relatives, there were 22 others seen who did not meet the criteria of being a parent, sibling, or child of a glaucoma patient, but who came from families with a family history of glaucoma. The results of the test procedures for these 22, using the same criteria of classification, are recorded in Table 4.

While the percentage of abnormalities was less in this group than in the previous one, it was much higher than in the normal population, particularly with respect to outflow facility. After water, 28 percent (12/43) of the eyes of these "distant" relatives of glaucoma patients had some impairment of outflow. The average outflow facility after water was 0.231 ± 0.077. This is significantly lower than the normal average, ($t = 4$).

SUMMARY

The results of a study of 110 close relatives of patients with chronic simple glaucoma were compared with the results of test procedures in the normal population. The prevalence of an intraocular pressure of 30 mm. Hg or higher was 5.5 percent for the entire study group and 9.7 percent for the

relatives 40 years of age and older. An abnormally elevated intraocular pressure after water, that is, higher than three standard deviations from the normal mean, was found in 9.1 percent the total group and in 16.1 percent of the group 40 years of age and older. Of the study population, 16.4 percent had facilities of outflow which were impaired more than three standard deviations from the normal mean. This degree of impairment occurred in 22.5 percent over the age of 40 years.

The average values for the entire group for pressure and outflow facility were significantly different than those for the normal population, with the intraocular pressure being higher and facility of outflow lower. By means of the ratio Po/C after water greater than or less than 100, it was possible to form two groups, with the Po/C $\geq$ 100 group comprising 40.0 percent of the population studied.

640 South Kingshighway (10).

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Ophthalmic Miniature

My friend, Professor v. Graefe, has, within the last three or four years, discovered the important fact that the excision of a portion of iris diminishes the intra-ocular pressure, a fact of pregnant interest in many diseases of the eye, and which he has applied with consummate skill to the treatment of glaucoma, of certain staphylomata, and last autumn to that of conical cornea.

Mr. William Bowman,
Royal London Ophth. Hosp. Reports, **2**:160, 1859-1860.

BITOT SPOTS*

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AND
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In many parts of the world Bitot spots are common conjunctival lesions, but they are quite unfamiliar to American ophthalmology. It may be of interest, therefore, to summarize recent studies of these lesions in Ethiopian school children and on the basis of the results to indicate the poor specific correlation of Bitot spots to vitamin-A deficiency. These observations were obtained as part of a comprehensive nutritional survey which will be referred to later.

A total of 1,790 children from three schools in Addis Ababa were inspected; 51 had Bitot spots—an incidence of 3.3 percent of the males and 1.8 percent of the females. There was a wide range of ages, with an average of 12.3 years; this was not different from the average age of subjects without Bitot spots. Although the diet of these children was inadequate in several respects, physical examinations in general did not indicate particular deficiencies.

Macroscopic and slitlamp examinations were performed by the same observer (D.P.) on 34 students with Bitot spots and 183 students without the spots. Compared to the bulbar conjunctiva of healthy American school children, the eyes of all of these Ethiopian children showed alterations. A grading system was established to estimate the degree of conjunctival wrinkling, roughness, and dryness in each student of the Bitot and non-Bitot groups. The data showed no significant difference between these groups. A large majority of the children had pingueculas which were readily distinguished from Bitot spots and were not related to the recorded severity of conjunctival changes. There was no corneal xerosis.†

Bitot spots, grossly visible and generally bilateral, were almost invariably located near the temporal limbus and showed considerable variation in size, substance and configuration (Plate I). The spots had a slightly refractile silvery-gray hue and a foamlike quality of their surface. Some of the larger lesions were triangular or eliptical; the smaller ones were pinhead-sized flecks of foam. Although in some cases conjunctival pigmentation and dilated vessels occurred in relation to the lesions, these were not constant associations. Many of the spots were compact plaques while others were lusterless conjunctival patches sparsely streaked with foam. The lesions were not altered by rubbing over the closed lid but, if scraped directly with a spatula, most of the foam could be removed, leaving a chalky conjunctival bed with wrinkled surface. Smears of Bitot spot material showed masses of xerosis bacilli and keratinized epithelial debris.

Night vision was tested with a radium plaque device (American Optical Instrument Company, U. S. Navy specifications) which was modified so that two neutral density filters could be used separately or in combination to diminish the test object intensity. Much "black-out" material was required to

* From the Ophthalmology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Public Health Service, U. S. Department of Health, Education and Welfare, Bethesda, Maryland (Dr. Paton) and the East African Institute for Medical Research, Mwanza, Tanganyika (Dr. McLaren). This paper is published with the approval of the Interdepartmental Committee on Nutrition for National Defense. This study was part of the Ethiopian Nutrition Survey and subsequent follow-up studies sponsored by the ICNND September, December, 1958; and March, June, 1959.

† Keratomalacia, moreover, is said to be rare in Ethiopia.

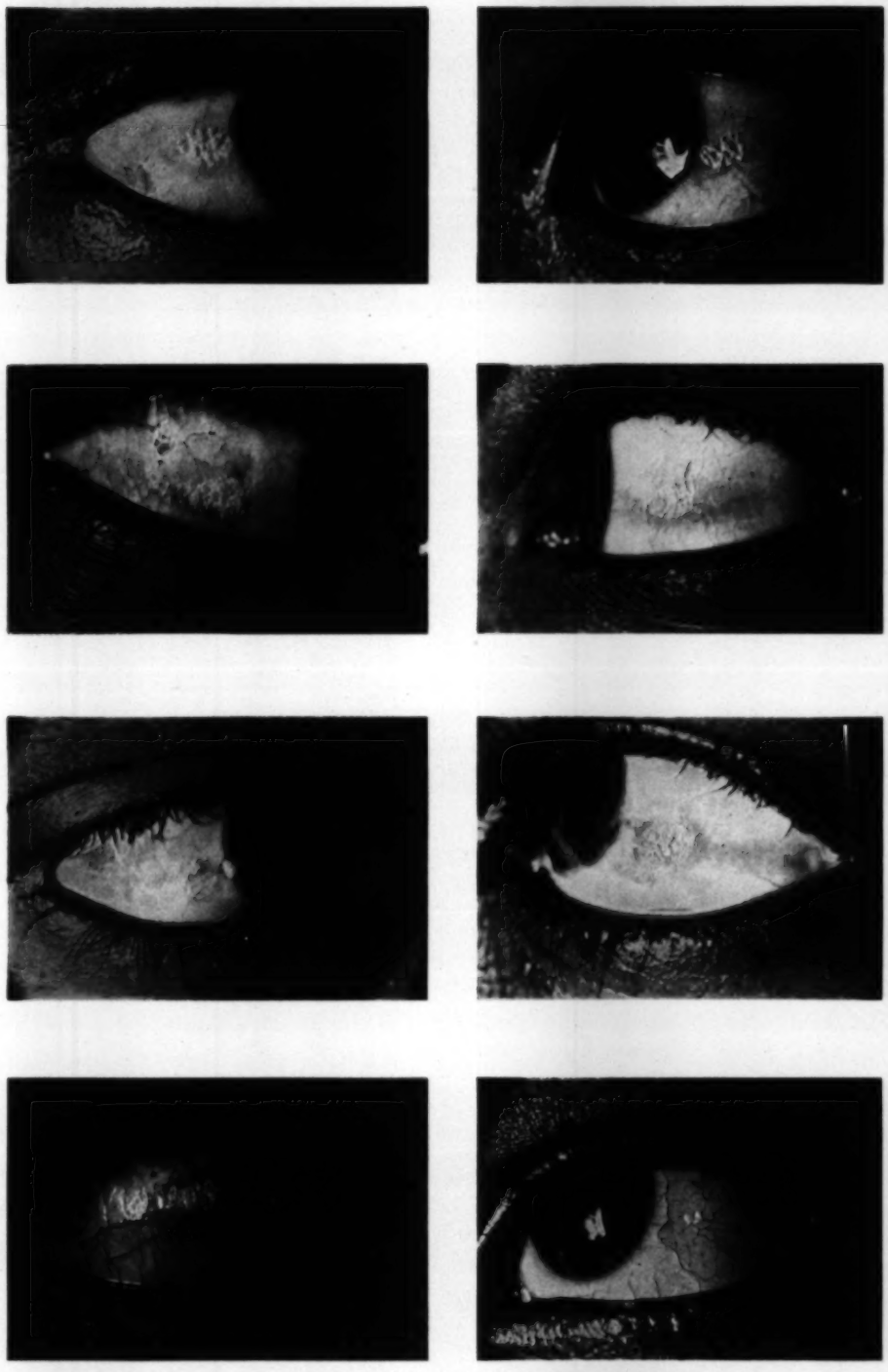

Plate I (Paton and McLaren). Bitot spots in Ethiopian children.

obtain almost total darkness in the schoolrooms available for night vision testing. In this section of the study there were 244 children of whom 28 had Bitot spots. Individuals were separately examined following 30 minutes to an hour of dark adaptation in groups of 15 to 25 students. The subject's forehead was a standard distance of 19 inches from the plaque and for each stimulus intensity he was required to give three consecutively correct statements of the test object's position before being credited with accurate perception. A short practice session prior to the dark-room examination gave surprisingly excellent comprehension of the procedure's requirements. A small red fixation light above the test object was used to facilitate peripheral perception of the radium plaque's "T" which was arbitrarily rotated. The results, when compared with those of a control group of 77 American school children using the same machine and under the same test conditions showed no abnormality of what was virtually the final visual threshold.

Serum vitamin-A and carotene levels were obtained from 76 students, 31 of whom had Bitot spots. Although there were occasional patients from each group with low values for either or both of these titers, there was no significant difference between the Bitot and non-Bitot groups. Severity of conjunctival wrinkling, roughness and dryness also failed to show a correlation with the serum levels.

The above summary has been taken from studies performed in March, 1959. The Ethiopian survey also included three other field examinations of the same student population—September 1958, December 1958, and June 1959. Many students, both with and without Bitot spots, had several determinations of their serum vitamin-A and carotene levels. For the most part, students with Bitot spots at the first examination retained the spots during subsequent examinations. A total of 911 separate vitamin-A and carotene determinations were obtained during the four examinations. Of these 422 were from Bitot spot subjects and 469 from students without the spots. As will be indicated in the Ethiopian survey report, there was no statistically significant difference in the mean blood levels of these two groups. The interested reader is referred to that report for details of the entire nutritional survey.*

Discussion

During the past century clinical description of Bitot spots has been amply provided, but there have been few illustrations of these lesions in journals of American ophthalmology. Two types of spots are described in the literature—those with and those without a foamy appearance. The nonfoamy variety has been compared to a "dab of chalk paste striated with a pin."[1] It has been postulated that the foam-covered spots are acutely acquired while the others are chronic but there is little evidence to support this view. Each type may be peculiar to the population in which it is found.[2] Only the foam-covered type was found in the Ethiopian children. Bitot spots are predominantly childhood lesions but may also be found in adults. Their customary preponderance in males has not been satisfactorily explained. Generally the spots are bilateral and located near the temporal limbus where, for anatomic reasons, there is the least lid pressure upon the bulbar conjunctiva. Exposure must be instrumental in the development of the spots. One report refers to a case of unilateral coloboma of the upper lid; there was a Bitot spot on the exposed portion of the globe at the 12-o'clock position.[3]

Bitot in 1863[4] first described conjunctival spots associated with night blindness. Classical contributions to the description of these spots and of conjunctival and corneal xerosis were made by Pillat.[5] There have been many efforts to prove or disprove the relationship of Bitot spots to vitamin-A de-

* Ethiopian Nutrition Survey. Report by the ICNND, September, 1959, National Institutes of Health, Bethesda, Maryland.

ficiency. Some of the pertinent and more recent literature on this subject will be referred to here. Night blindness, conjunctival and corneal xerosis, and keratomalacia can be produced in vitamin-A deprived animals, and these changes in both animals and humans have been shown to reverse with vitamin-A therapy.

Bitot spots have reportedly occurred in 10 rabbits and one monkey maintained on a diet in which the main deficiency was intended to be vitamin A,[6] but they have not been observed in controlled human studies of vitamin-A deprivation.[7]

Clinically, some authors have reported disappearance of the spots with nutritional improvement and sometimes with vitamin A alone;[8–12] others have found little or no effect of vitamin-A therapy.[1–3, 13–17, 24] Often vitamin A alone has not been used and therapeutic response cannot be attributed solely to the vitamin.

One of the most specific signs of vitamin-A deficiency is reversible impairment of night vision. In some reports Bitot spots have been accompanied by night blindness, but in the majority of studies of the spots it has either not been sought or has not been present. This could be variously interpreted as showing: no direct relationship of Bitot spots to avitaminosis A; or that certain individuals may manifest either or both of these signs in the presence of vitamin deficiency; or that techniques of detecting hemeralopia were not satisfactory.

The difficulty of meaningful night vision testing in field studies of uneducated populations makes this examination an impractical diagnostic tool in large surveys.

Recently, omitting night vision testing, a mass survey of inhabitants of Ruanda-Urandi was performed for appraisal of vitamin-A deficiency as evidenced by Bitot spots.[18] Although there was no individual correlation of blood vitamin-A levels with the presence or absence of the spots, there was a slightly lower average of blood vitamin level in the total group of affected persons. Rather than showing a specific Bitot spot-vitamin A correlation, the results could instead reflect a lower nutritional status of persons with the spots.

As a rule Bitot spots are a sign of nutritional deficiency because they are almost always found in poorly fed populations; only rarely do healthy persons of normal nutritional status show these lesions. Bitot spots have been reported in European prisoners of war[19] as well as in undernourished children in this country and Europe. Avitaminosis A occurs rarely in adults due to extensive tissue storage of this vitamin but is more common in young children where storage is more limited.[20] It had been hoped that all of the children in the present investigation would receive daily vitamin-A therapy over a four-month period. Obstacles to proper administration of the vitamin capsules arose which have delayed completion of this part of the study. Therefore, the significant question of whether these Ethiopian Bitot spots would respond to vitamin-A therapy has not yet been answered. This work, by Ethiopian investigators, is now in progress.

Bitot spots are accompanied by conjunctival xerosis—a keratinizing metaplasia of the epithelium[20]—but the clinical appearance of xerosis is not necessarily dependent upon vitamin-A deficiency.[18] Histologically, too, there is no specific sign of avitaminosis A. One author writes, ". . . there exists no morphological alteration of tissue which alone can be considered strictly pathognomonic of vitamin A deficiency."[20] In fact, keratinization of normal conjunctiva shows such variation that epithelial scrapings have not been considered useful in the diagnosis of vitamin-A deficiency.[21]

The pathology of Bitot spots has been described by several authors.[22, 20] This includes keratinization of the epithelium, Meibomian secretion, and edema of the mucosa and submucosa; the main bulk of the lesion is Cornybacterium xerose. The foamlike quality of these lesions has been variously at-

tributed to gas production by saphrophytic organisms or to the extensive edematous changes of the affected tissue.

In the survey of Ethiopian school children, the presence of Bitot spots was not related to variation of concentration of vitamin A in the blood nor to the severity of xerotic changes of the conjunctiva—although some degree of these tissue changes was always present. In concluding that no current vitamin-A deficiency could account for the presence of Bitot spots, one assumes that the blood titer reflects vitamin availability at a cellular level. This is probably a valid assumption, for all 244 of the children tested showed universally normal performance on night vision testing, and general physical examinations showed no indication of avitaminosis A.

The following comment by Dr. William J. Darby, director of the Ethiopian survey, is pertinent: "It is of interest that the carotenoid pigments were in considerable concentration in the blood of these (and other) Ethiopian children. Chromatographic studies indicated a remarkably high concentration of non-β-*carotene* pigments. Whether this observation might relate to tissue availability of vitamin A for certain cellular functions may be a point worthy of consideration in future investigations."[23]

Nothing can be said from the present study about the influence of climate, exposure, hygiene, racial factors or peculiarities of bacterial flora on the genesis of Bitot spots. Poor nutrition, rather than vitamin A deprivation per se, is probably the basic inciting factor. This conclusion, even supported by failure of vitamin-A therapy in Bitot-spot patients, has been previously elaborated[2] and later supported by a number of case reports. The role which vitamin-A deficiency may sometimes play in the occurrence of Bitot spots must not be discounted. If, in the presence of nutritional inadequacy, there is an important component of vitamin-A deficiency (demonstrable by hemeralopia or low blood levels) such patients with Bitot spots may be the ones whose spots regress rapidly with vitamin-A therapy.

Summary

1. The incidence and clinical description of Bitot spots occurring in Ethiopian school children is presented.

2. Although these lesions are considered evidence of poor nutrition, no correlation with vitamin-A deficiency has been demonstrated.

The Johns Hopkins Hospital (5).
East African Institute
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Acknowledgment

We wish to indicate that the planning, direction, and organization of this survey were under the guidance of Dr. William J. Darby, Vanderbilt University School of Medicine, and Dr. Arnold E. Schaefer, Executive Director, ICNND, Bethesda, Maryland.

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GROSS AND MICROSCOPIC PATHOLOGY IN AUTOPSY EYES*

Part II. Peripheral chorioretinal atrophy

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It has long been recognized that in the process of aging, depigmentation and atrophy of the peripheral choroid is a common finding.[1] This occurs as a diffuse zone of lesser pigmentation encircling the globe between the equator and the ora serrata. However, it has not been emphasized that discrete punched-out areas of depigmentation also accompany the aging process. Recently a pathologic study of an eye containing many of these lesions was reported by Wolter and Wilson.[2] Because of the magnitude of the lesions in this eye, it would present little if any difficulty in proper ophthalmoscopic interpretation. However, in its earlier stages of development this type of lesion is not infrequently confused with an inactive chorioretinitis. With the development of greater skills in indirect ophthalmoscopy, these lesions are being seen more frequently. It is the purpose of this study to shed more light on their nature and significance.

Four hundred ninety-four consecutive autopsy eyes from 250 autopsies were studied with slitlamp magnification. Photographs were taken of the interesting gross pathology and these areas were then sectioned for microscopic correlation.† Approximately one-fourth of these eyes contained discrete atrophic-appearing lesions situated within a

* From the Department of Ophthalmology and the Oscar Johnson Institute, Washington University School of Medicine, Saint Louis, Missouri. The research relating to this study was financed in part by a research grant, B-1789, from the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, Public Health Service.

† See previous paper for more detailed description of method.[3]

TABLE 1

AGE DISTRIBUTION OF LESIONS

Age (yr.)	No. of Autopsies	Large†	No. of Patients with Lesions*			%
			Moderate	Minimal	Total	
0–1	42	0	0	0	0	0
1–20	20	0	0	0	0	0
20–40	18	0	0	0	0	0
40–50	26	0	4	4	8	31
50–60	40	2	4	7	13	33
60–70	51	3	6	13	22	43
> 70	53	12	7	6	25	47
TOTAL	250	17	21	30	68	27
> 40	170				68	40

* 63 of the 68 individuals with lesions had bilateral involvement (93%).
† Eye with largest lesion used for classification.

few mm. of the ora serrata (table 1). The lesions were almost always situated in the lower one-half of the globe, usually between the 5- and 7-o'clock positions. When situated elsewhere, there was almost always an associated greater amount of involvement inferiorly. Bilaterality was the rule, although the size of the lesions frequently varied in the two eyes. The incidence and the size of the lesions appeared to increase with age. No lesions were found in those under the age of 40 years (table 1). In this series, the incidence in males was approximately 50-percent greater than in females (table 2).

On gross examination the appearance of the lesions varied from a single round or oval depigmented spot of one mm. or less in diameter to large atrophic patches with irregularly scalloped edges. The larger lesions usually contained some residual pigment within them and moderately increased or normal amounts at their margins. They appeared to represent a confluence of the smaller lesions (figs. 1, 3, 7, 8, 9, 10, and 12).

Histologically the depigmented lesions were also sharply defined by an abrupt disappearance of outer retinal layers, including pigment epithelium, rods and cones, and outer nuclear layers. The inner retinal layers appeared somewhat compressed with an irregularity of the cellular pattern (figs. 2 and 4). The retinal blood vessels in most of the sections appeared normal. Bruch's membrane remained intact beneath the lesion (figs. 2, 4, and 5). The choroidal vessels were mainly replaced by fibrous tissue with little evidence remaining of their former existence. The choriocapillaris was, for the most part, absent, and when present, it was void of blood cells. The larger vessels were fewer in number, but those present were patent and not particularly sclerotic. The intervascular stroma was less cellular than normal and stained less densely than choroid elsewhere in the eye. The choroidal part of the lesion was not as sharply defined as the retinal, but was consistently associated with each retinal lesion examined (figs. 5, 6, and 13).

CORRELATIVE STUDIES

Attempts to correlate ophthalmoscopic findings with generalized and specific areas of atherosclerosis have been reported in the past.[4–6] Since autopsies were performed on all the individuals in the present study, it was possible to see how well the finding of

TABLE 2

SEX DISTRIBUTION OF LESIONS

Sex	No. of Autopsies	No. of Lesions	%
Male	146	47	32
Female	104	21	21

Fig. 1 (Okun). 58-411L. Isolated discrete oval area of depigmentation (A) just posterior to the zone of cystoid degeneration (C), approximately two mm. from the ora (O). "Small" lesion. (Black and white, copied from Ectachrome transparency.)

discrete areas of peripheral chorioretinal atrophy correlated with generalized atherosclerosis. The system used for grading atherosclerosis was as follows: At the time of autopsy the amount of involvement in the aorta, coronary, and cerebral arteries was grossly estimated by the pathologist as insignificant, slight, moderate, or advanced. A point system was devised in which one point was allotted for slight, two for moderate and three for advanced atherosclerosis. The points for each location were then totaled. A total of four to five points was considered moderate, six to seven advanced and eight to nine points, far advanced generalized systemic atherosclerosis.

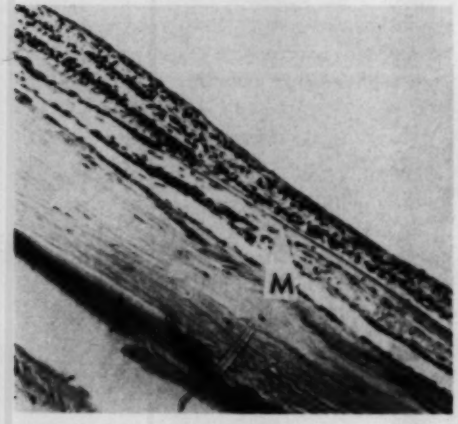

Fig. 2 (Okun). Section through lesion in Figure 1, showing abrupt cessation of outer retinal layers including pigment epithelium, rods and cones, and outer nuclear layers. Bruch's membrane (M) remains intact. (Elastic stain.)

Fig. 3 (Okun). 58-504. Area of depigmentation (A) with scalloped borders and adjacent spot (a) not yet merged with larger lesion.

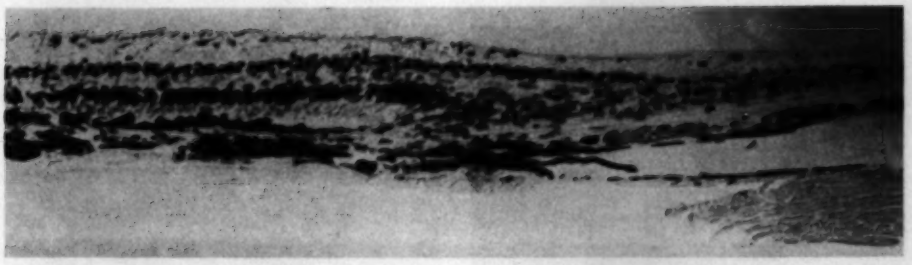

Fig. 4 (Okun). Section through lesion in Figure 3, showing arear of transition from normal to atrophic retina.

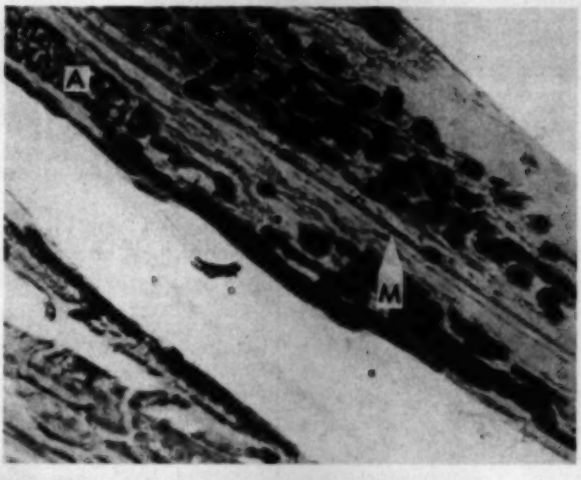

Fig. 5 (Okun). High magnification of atrophic area showing complete disappearance of choriocapillaris and replacement by fibrous tissue. Note normal appearing large choroidal vessel (A) and Bruch's membrane (M) which appears intact.

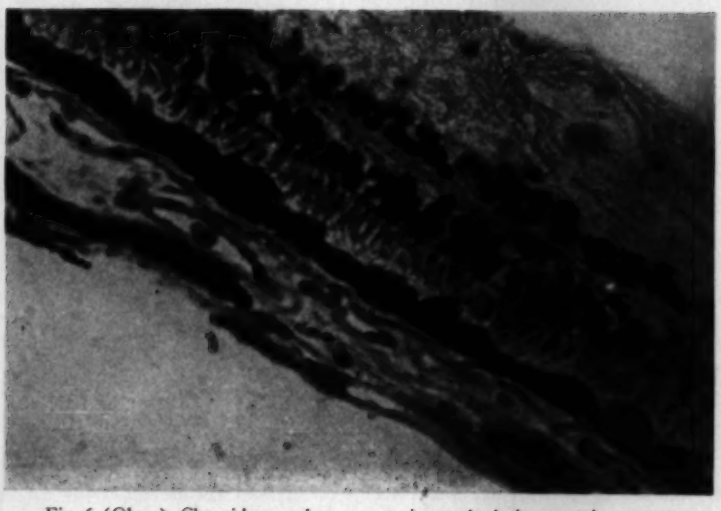

Fig. 6 (Okun). Choroid several mm. posterior to the lesion contains patent smaller vessels and choriocapillaris.

Fig. 7 (Okun). 58-440. "Large" lesion with small amount of residual pigment (P) in center of atrophic area.

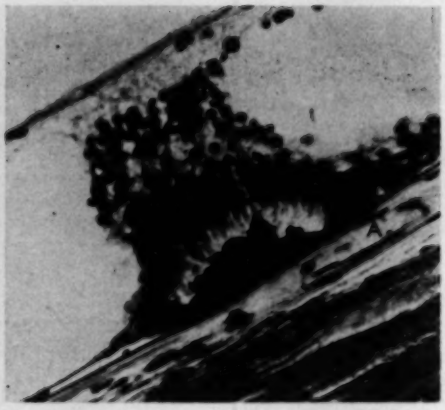

Fig. 9 (Okun). Section through residual pigment in Figure 7. In this area all other retinal elements are also present. Note patent vessel (A) underlying this area.

The chorioretinal lesions were also graded according to size as large, moderate, and minimal. The "minimal" group included the dotlike lesions at the ora as well as the isolated lesion of approximately one millimeter or less in diameter (figs. 1 and 10). The group considered as "moderate" was made

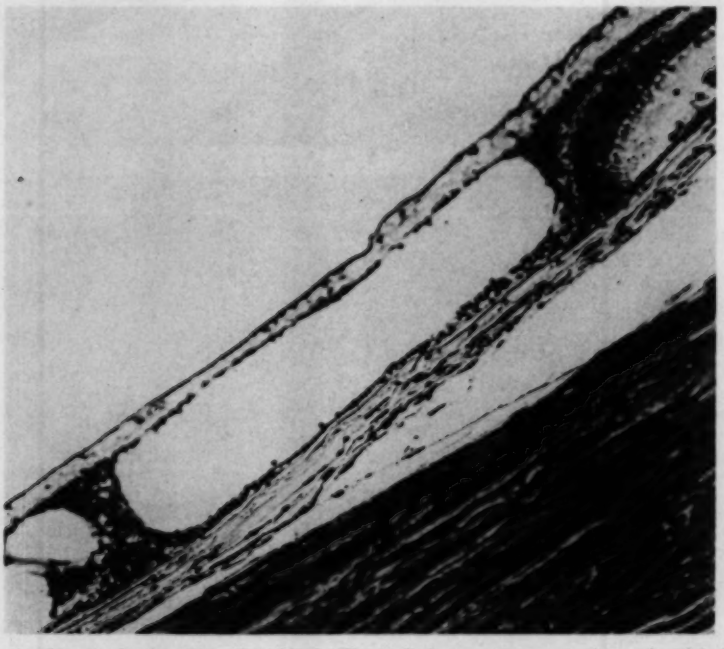

Fig. 8 (Okun). Section through lesion in Figure 7 shows appearance of margin of lesion within an area of cystoid degeneration.

up of eyes with an accumulation of several of the isolated lesions in the "minimal" group. The "large" lesions were those with the scalloped margins and were much larger than the lesions in the other two groups (figs. 3, 7, and 12).

The group of individuals with large lesions proved to be of most interest in this correlative study. Three of these 17 individuals (18 percent) had advanced systemic atherosclerosis, and 12 of the 17 (70 percent) had far-advanced atherosclerosis (table 4). In a matched series (consecutive series matched for sex and age within three years) of patients without chorioretinal atrophy only four of the 17 had far-advanced systemic atherosclerosis (table 5). This appears to be a statistically significant difference ($X^2 = 5.76$). However, it must be noted that these changes do occur mainly in the older age groups, where a greater incidence of atherosclerosis is expected (table 3).

As a clinical counterpart to this study, 30 patients from the Barnes Hospital medical wards were studied by indirect ophthalmoscopy with scleral indentation. Seventeen of these patients had bilateral areas of chorioretinal atrophy in the periphery (table 6). The appearance of the lesions thus observed was very similar to those observed in the formalin-fixed autopsy eyes. In some cases the base of the lesions had a pinkish appearance, probably due to the intact blood flow. However, in most of the cases the lesions appeared either whitish or yellow. They were usually located inferiorly, although two

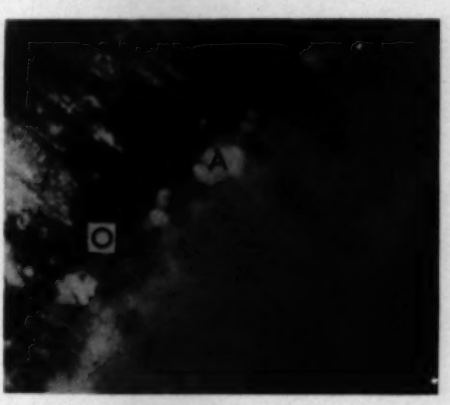

Fig. 10 (Okun). 59-474. Series of small discrete area of depigmentation (A) just posterior to the ora serrata (O), within the zone of cystoid degeneration.

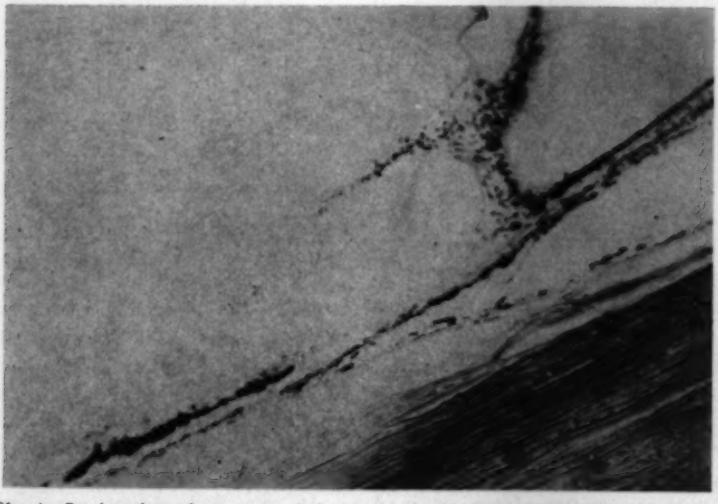

Fig. 11 (Okun). Section through an area of depigmentation as shown in Figure 10. Atrophy of outer retinal layers within area of cystoid degeneration.

TABLE 3

AGE DISTRIBUTION OF ATHEROSCLEROSIS IN AUTOPSY POPULATION

Age	No. of Autopsies	Mod. A.S.	Advanced & F.A.	Total	%
0–1	42	0	0	0	0
1–20	20	0	0	0	0
20–40	18	0	3	3	17
40–50	26	3	6	9	35
50–60	40	5	17	22	58
60–70	51	13	16	29	57
> 70	53	14	34	48	91
TOTAL	250	35	76	111	45

TABLE 4

ATHEROSCLEROSIS IN POPULATION WITH LESIONS

Type of Lesion	No. of Autopsies	Mod. A.S.	Adv. A.S.	F.A.	Total	%
Large	17	2	3	12	17	100
Moderate	21	6	5	5	16	76
Minimal	30	5	5	4	14	47

TABLE 5

ATHEROSCLEROSIS IN POPULATION WITH LARGE LESIONS COMPARED WITH MATCHED SERIES OF CONSECUTIVE CASES (MATCHED FOR AGE AND SEX) WITHOUT LESIONS

	No. of Autopsies	Far Advanced A.S.	X^2
With large lesions	17	12	5.76
Without lesions	17	4	

patients in this group had isolated lesions elsewhere.

TABLE 6

CLINICAL SURVEY WITH INDIRECT OPHTHALMOSCOPY

Age (yr.)	No. of Patients	No. of Patients with Lesions	%
0–1	0	0	0
1–20	2	1	50
20–40	1	0	0
40–50	8	6	75
50–60	5	5	100
60–70	9	1	11
> 70	5	4	80
TOTAL	30	17	57

COMMENT

The primary disease appears to be an obliteration of smaller choroidal vessels leading to disappearance of the choriocapillaris and subsequent atrophy of the outer retinal layers. This histologic picture is not unlike that described by Ashton in a case of central areolar choroidal sclerosis.[7] As is pointed out in this paper, the pathogenesis of such a histologic picture is a matter of conjecture. A number of possibilities are mentioned including the various types of occlusive phenomena as well as primary or secondary vascular atrophy.

The best evidence for occlusive disease would, of course, be the demonstration of the occluded vessel on histologic section. In the present study no areas of arterial occlusion were observed about the atrophic lesions, so the evidence for occlusive disease can only be presumptive.

It was first shown experimentally by Wagenmann in 1890 that sectioning short

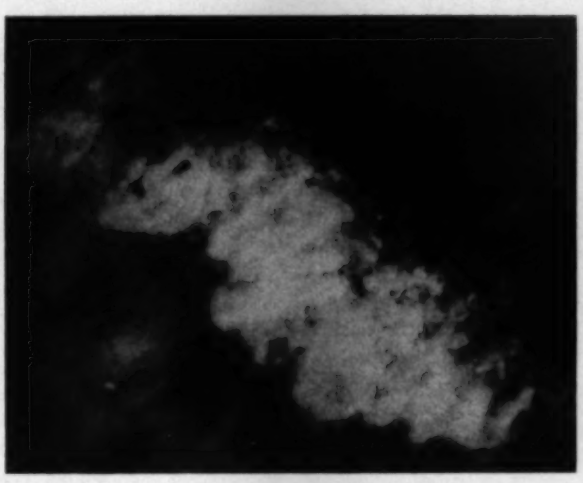

Fig. 12 (Okun). 58-497. Zone of depigmentation with scalloped margins just posterior to the ora. This appears to be a more advanced stage of the changes shown in Figure 10.

posterior ciliary arteries in the rabbit produced areas of chorioretinal atrophy.[8] Coats (1907) and Hepburn (1912) have presented further clinical arguments in favor of a sectorial arrangement of choroidal blood supply with vessels acting as though they were end arteries.[9,10] If this be the case, the totally or partially occluded vessel may be some distance from the lesion, thus making its detection even more difficult. The retrobulbar region in many of the eyes examined in this study contained vessels showing advanced atherosclerosis as well as an occasional totally occluded artery.

Evidence against the production of lesions on the basis of occlusion of short posterior ciliary arteries alone was presented by Wybar in 1954. By means of Neoprene in-

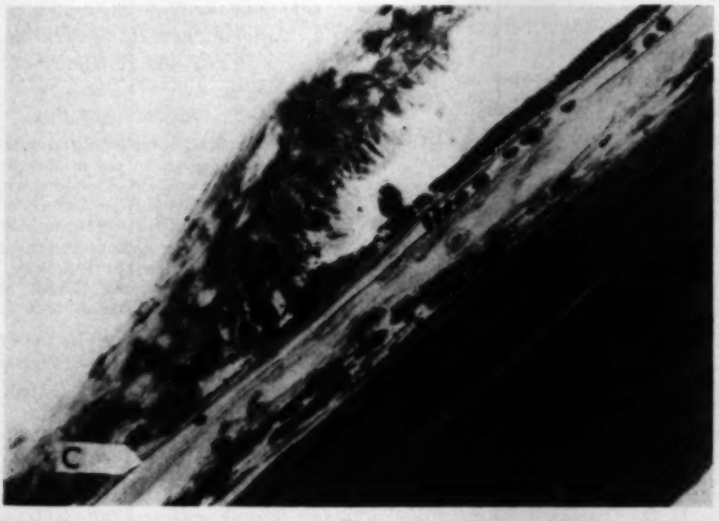

Fig. 13 (Okun). Section through lesion shown in Figure 12 showing transition zone. The choriocapillaris (C) appears patent, but blood cells are present primarily under the more normal appearing retina.

jection studies in human eyes, he has shown that it is possible to fill the entire choroid via the ophthalmic artery despite ligation of a posterior ciliary artery. In one eye he was able to fill two-thirds of the choroid via a single short posterior ciliary artery.[11] This proves that at least in certain eyes anatomic conditions favor good collateral flow, which nevertheless does not guarantee against infarction.

The inferior location of these lesions may likely be related to closure of the fetal fissure with greater vascular variation and less reserve in this region, though this has yet to be shown.

In conclusion, the information gathered in this study indicates that the discrete punched-out appearing areas of depigmentation represent a degenerative rather than an inflammatory process. Favoring a degenerative process were the following observations:

1. An increasing incidence with age with no lesions in individuals under the age of 40 years.
2. A positive correlation between the size of the lesion and the degree of generalized atherosclerosis.
3. A positive correlation between the size of the lesion and age.
4. A rather constant inferior location.
5. Usual bilateral involvement.
6. The histologic picture with Bruch's membrane intact.

The associated finding of severe atherosclerosis in 88 percent of the 17 individuals with large chorioretinal lesions needs further study. This may be a reflection of the older age group in which the larger lesions are found. On the other hand, its presence on ophthalmoscopic examination may prove to be an additional means of evaluating the extent of generalized systemic atherosclerosis.

Summary

1. Discrete punched-out appearing areas of depigmentation in the peripheral fundus were observed in approximately one fourth of 494 consecutive autopsy eyes studied by slitlamp magnification.

2. Histologically they represent areas of chorioretinal atrophy with obliteration of the choriocapillaris. The primary disease appeared to be vascular in nature, leading to probable occlusion and disappearance of smaller choroidal vessels.

3. The degenerative nature of these lesions is supported by the following factors: (a) increasing incidence and size with age, (b) almost constant bilateral involvement in inferior one-half of the fundus.

4. Eighty-eight percent of the individuals with larger lesions had severe systemic atherosclerosis. This association may prove to be of clinical value in evaluating the extent of atherosclerosis.

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National Institute of Neurological Diseases and Blindness (14).

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I wish to acknowledge with gratitude the aid and encouragement given to me in this study by Dr. Bernard Becker and Dr. Theodore Sanders. I am indebted to the Washington University School of Medicine, Pathology Department, for making available the autopsy findings for correlative studies, and lastly to the eye pathology technicians, Mildred Curtis, Cleopatra Galvin, and Yvonne Gathright, for their assistance.

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EXPERIMENTAL CORNEAL ALLERGY*

Correlation between clinical and serologic findings

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Introduction

The allergic nature of the "disease of the graft" has reawakened interest in corneal allergy which was studied originally at the beginning of the century. It was found by Wessely,[1] in 1911, that a single intracorneal injection of a small dose of horse serum is followed after 12 to 14 days by a typical ring-shaped opacity in the cornea and by iritis. Histologically the opacity consisted of infiltration of leukocytes. Morawiecki,[2] in 1948, compared the ring opacity of the cornea with the precipitation of antigen and its specific antibody in agar plates. The origin of the antibody in the Wessely phenomenon is not known. Morawiecki could not find any relation between the appearance of the corneal opacity and the antibody titer in the serum of his experimental animals. Breebart and James-Witte,[3] following the method of von Szily,[4] in 1959, described ring form opacity in rabbit corneas after repeated intracorneal injections of diluted horse serum.

The purpose of this study was to determine the relationship between serum antibody titer and corneal changes in these allergic manifestations. With this end in view, the Wessely reaction was chosen for study; with the modification that instead of horse serum pure solutions of various proteins were injected.

Materials and Methods

As experimental animals we used rabbits from a mixed stock, weighing approximately 2.0 kg. As antigens 0.1 ml. of the following protein solutions were injected.

	Gm. %	In No. Rabbits
Egg albumin	4	1
Human albumin	2.5	2
Human gamma globulin in concentration of:		
	8	2
	4	2
	2	2
	1	2
	0.5	2
	0.1	2

All proteins were dissolved in physiologic salt solution. In four control animals physiologic salt solution, autogamma globulin and rabbit gamma globulin were injected. The rabbits were anesthetised with pentobarbital and ether. The eyes were proptosed by pres-

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sure with forceps. About 0.1 ml. of the solutions was injected into the cornea with a fine No. 25 needle.

It has to be stressed that it was difficult to inject an exact quantity of fluid. Because of the compactness of the corneal lamellae, part of the solution may flow out from the cornea along the path made by the needle.

Following the injection, each rabbit was examined with the slitlamp daily or even twice daily. The rabbits were bled every three to five days, the sera collected, stored at −20°C., and the antibody titer determined at the end of the experiment in all sera at the same time.

Antibody determinations

All sera were inactivated in a 56°C. waterbath for 20 minutes. The antigamma globulin titer was determined by adding to doubling dilutions of the serum a suspension of human erythrocytes coated with incomplete anti-Rh antibodies. One drop of the sensitized cells was added to 0.2 ml. of the serum dilutions. The mixture was centrifuged for one minute at 1,000 rpm and the tubes examined for agglutination. The coating of the cells with anti-Rh antibodies was performed as follows:

Equal parts of anti-Rh serum with incomplete antibodies of a titer of 1:8 and a five-percent red blood cell suspension (O,RH+) were incubated in a 37°C. waterbath for 30 minutes. The cells were then washed three times in large amounts of normal saline and used for the titrations.

The antihuman albumin titer was determined by the tannic acid hemagglutination method as described by Witebsky and Rose.[5] As antigen, a 0.1-percent dilution of human albumin was used.

Results

The clinical reaction was very similar in each animal and similar to what was described by previous authors. The initial haze produced by all intracorneal injections disappeared after a few hours. No reaction

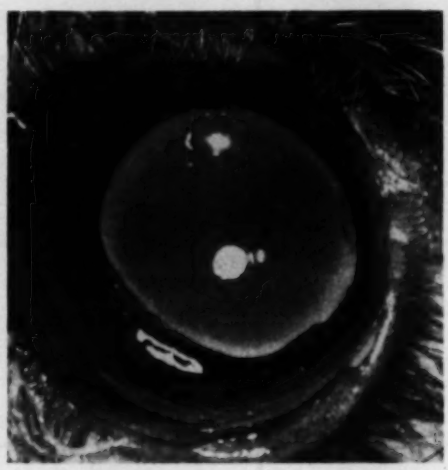

Fig. 1 (Nelken, et al.). Stage 2 of the experimental allergic keratitis. Ring opacity accompanied by dark engorged blood vessels at the periphery.

appeared in the corneas of the control animals. The reaction in the other animals appeared usually on the fifth to eighth day following the injection and as will be seen invariably coincidentally with the first rise in the serum antibody titer. The clinical reaction to begin with manifested itself by injection of the limbal blood vessels and by iritis. This initial reaction we termed Stage 1. With a single exception this stage appeared in all animals. Stage 2 manifested itself by a corneal haze. It appeared one to 16 days after Stage 1. It took very soon the pattern of the well-known ring opacity, being situated like the gerontoxon inside the limbus and associated with vessels in the periphery (fig. 1).

The time interval between the two stages and the intensity of stage 2 were dependent on the amount of antigen injected and the serum antibody titer. The higher the titer, the more intense the opacity and the quicker its appearance. In animals with low antibody titer, the circular haze at the periphery did not form a complete ring. In some animals with very low titers this stage was not even reached.

In most animals within three days of the

Fig. 2 (Nelken, et al.). Stage 3. Dotted opacity.

onset of stage 2 the ring opacity in the cornea and the vascularization became rapidly fainter leaving behind a dotted opacity in the form of a triangle or quadrangle. This we called Stage 3 (fig. 2). In animals in which the antibody titer was low the cornea cleared completely and stage 3 was not reached. Typical examples of the parallelism between the serum titer changes and the clinical reaction are shown in Tables 1, 2, and 3. All the results are summarized in Table 4.

Comment

It is apparent from Tables 1, 2, and 3 that there was a very clear parallelism between the rise in the serum antibody titer and the appearance of the corneal changes. This parallelism was present in all the animals in whom the clinical reaction appeared.

It will be noted from Table 4 that the serum antibody titer at a given stage in the clinical reaction was not the same in all the animals.

Although there is a general relationship between the amount of antigen injected and the amount of antibody formed it will be noted that this relationship varied from animal to animal. This can be explained by individual variability of antibody production or by escape of antigen from the cornea during injection.

The antibody titers against the human albumin were higher than the titers against human globulin. This result is explained by the greater sensitivity of the method which was used for the determination of antihuman albumin antibodies.

TABLE 1

RABBIT 4: ANTIGEN INJECTED: HUMAN GAMMA GLOBULIN (4.0 GM. PERCENT)

Time (da. following injection)	Serum Antibody Titer	Clinical Reaction
1	0.00	
5	0.00	
7	1:80	
8		Stage 1
10	1:80	
15	1:60	Stage 2
16	1:80	
19	1:80	
35	1:10	Stage 3

TABLE 2

RABBIT 12: ANTIGEN INJECTED: HUMAN GAMMA GLOBULIN 0.1 GM. PERCENT

Time (da. following injection)	Serum Antibody Titer	Clinical Reaction
6	0.00	Stage 1
8	1:30	
9	1:30	
15	1:40	Stage 2
19	1:30	
22	1:10	Reaction disappears
27	1:5±	Cornea clear

Summary

1. The Wessely reaction was produced in rabbits by injecting various amounts of foreign proteins intracorneally.

2. The clinical reaction is shown to express itself in three stages which are described.

TABLE 3

RABBIT 13: ANTIGEN INJECTED: HUMAN ALBUMIN 2.5 GM. PERCENT

Time (da. following injection)	Serum Antibody Titer	Clinical Reaction
1	0.000	
2	0.000	
9	1:160	Stage 1
12	1:640	
15	1:1280	Stage 2
19	1:1280	
21	1:1280	
31	1:640	Fading of opacity

TABLE 4

ANALYSIS OF FINDINGS

Rabbit No.	Antigen Injected	Maximum of Serum Antibody Titer	Stages of Clinical Reaction
	Human Gamma Globulin in Concentration of (gm. percent)		
1	8.0	1:3000	1 2 3
2	8.0	1:1000	1 2 3
3	4.0	1:160	1
4	4.0	1:160	1 2 3
5	2.0	1:40	1
6	2.0	1:20	No reaction
7	1.0	1:60	1 2 3
8	1.0	1:120	1 2 3
9	0.5	1:80	1 2
10	0.5	1:10	1 2
11	0.1	1:60	1 2
12	0.1	1:40	1 2
	Human Albumin in Concentration of (gm. percent)		
13	2.5	1:1280	1 2
14	2.5	1:1560	1 2 3
	Egg Albumin in Concentration of (gm. percent)		
15	4.0	0	No reaction

3. The serum antibody titer was measured in each animal.

4. It was found that there is a dependence between the serum antibody titer and the various stages of the clinical reaction.

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THE ROLE OF BRAIN DAMAGE IN CONGENITAL DYSLEXIA*

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Dyslexia is a syndrome characterized by the inability of a child to learn to read at normal grade level even though the child has normal or superior intelligence. There are many factors which contribute to the development of the dyslexic patient. The respective roles of ophthalmology, psychiatry, neurology and education, as they are associated with these contributing factors, were reviewed in an earlier publication.[1] Since then our interest has been further stimulated to investigate some of these basic problems of

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congenital dyslexia. A classification by Rabinovitch[2] divides the retarded reader into two major groups:

1. The exogenous group, in which the reading disability is due to psychiatric and educational factors.

2. An endogenous group, in which (a) there was frank brain damage which might result in the child with cerebral palsy; (b) a group in which there was no demonstrable neurologic lesion but yet there was a basic incapacity to interpret written material and an inability to associate concepts with symbols.

In Subgroup 2(b) there is no demonstrable organic neurologic lesion present, yet there is this basic incapacity to interpret written material. It is with reference to this group that there has been much romance and conjecture. Vision, ocular muscles, ductions, convergence insufficiency, convergence excess, heredity, cerebral dominance, blood dyscrasia, hypothyroidism and many other equally unsubstantiated factors, all have had some temporarily popular role in the etiology of the dyslexic patient.

To understand the problem better, brief reference is made to the anatomy of the region involved.[3] There are six areas of anatomic importance in reading. Reading is first a matter of vision, or sensation, and secondly an interpretation, or perception, of what is seen. Images are recorded on the retina and then transmitted as electrical impulses to the optic nerve and then, via the lateral geniculate body, to the calcarine fissure in the occipital lobe. This is the primary visual receptive area 17 of Brodmann.

Surrounding area 17 are the secondary and tertiary (fig. 1) visual cortical areas 18 and 19 of Brodmann. Area 18 lies immediately adjacent to area 17, surrounding it like a reversed letter "C". This area is activated only by impulses starting in area 17 and is concerned only with visual memory patterns for the visual recognition of objects. Destruction of this area results in loss of ability to recognize objects—visual agnosia. The ability to recognize symbols of language, that is, the ability to read, is not affected.

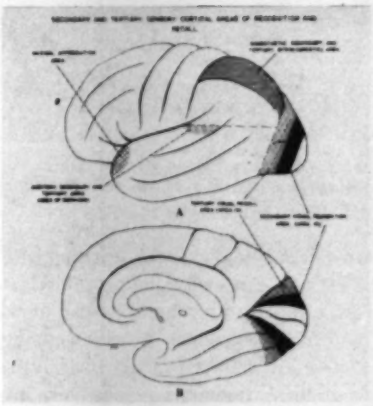

Fig. 1 (Goldberg, Marshall and Sims). This diagram illustrates the secondary and tertiary reception areas of the cerebral cortex.

The tertiary visual cortical area is area 19. This area lies immediately adjacent to area 18 and surrounds it on the medial and lateral surface of the occipital area like a reversed capital letter "C". This area is stimulated by area 18. It is concerned with the elaboration of memory patterns necessary for the recall of language symbols. Destruction of area 19 impairs memory recall of objects, persons and language. A lesion of this area may impair the ability to read. The angular gyrus, located in the posterior part of the parietal lobe and lying adjacent to area 19, serves the same function for language symbols that area 19 performs. The angular gyrus is essential in both reading and writing. The area of Wernicke, concerned with the recognition and recall of speech by its connections to the angular gyrus, reinforces by auditory stimuli the ability to understand written language. The anatomic complexity of reading is further demonstrated by those individuals whose silent reading is associated with lip movement. In such individuals the ability to read will depend on the motor speech area of Broca and its connections with the angular gyrus.[4]

Lesions of either Wernicke's area or

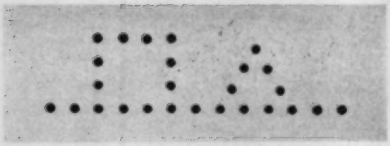

Fig. 2 (Goldberg, Marshall and Sims). Gestalt psychology emphasizes that we perceive configurations.

Broca's area complicate the learning of reading. This is especially important when the educator and reading therapist use the classroom techniques, which involve hearing the spoken word and repeating what is heard. Both of these functions respectively involve Wernicke's area and Broca's area.

A word should be said about visual interpretation, or perception.[5] This involves a "putting together" of the visual impulses. This is a gestalt phenomenon which arises by a perception of the whole pattern: a photograph is recognized as a whole and not by the separate features. The figure of the triangle and square is an example of gestalt psychology (fig. 2). We do not perceive a series of isolated dots; rather we perceive a square and triangle sitting on a line. The dots are organized in perception so that they are seen as a configuration. General psychologic disturbances or subclinical brain damage may impair this interpretation of the peripheral stimulations into visual perceptions. It is in this perceptive area that some of our patients show a deficiency.

This anatomic basis of alexia is well substantiated by the number of case histories which show a relationship between alexia and cerebral pathology. The pathology is in the parietal occipital area. Further evidence showing the similarities of acquired alexia to congenital dyslexia is suggested by psychologic testing, by the lack of success encountered in remedial training with the standard remedial teaching techniques, and by electroencephalographic changes.

Kawi and Pasamanick[6] reviewed the prenatal and paranatal records of 205 children with reading retardation and found that 16.6 percent had been exposed to two or more maternal complications as compared with 1.5 percent of a similar group without reading disorders. The complications were such that contributed to fetal anoxia. It was their hypothesis that severe brain damage led to stillbirth, abortion and neonatal death; and then, in a descending gradient, lesser forms of injury led to cerebral palsy, epilepsy and behavior disorders; while the most benign form of brain damage was associated with speech disorders and congenital dyslexia.

Penfield and Hécaen[7] reported 17 cases of adult patients with focal epilepsy. Partial resection of the parietal occipital cortical area was performed because of epilepsy. Subsequent examinations revealed no impairment of the intellectual capacity; the EEG showed abnormalities similar to those which are reported in our patients with dyslexia, and visual-motor psychologic responses were the same as seen in cases of congenital dyslexia. Defects of perception were present. Careful psychologic examination of the visual-motor functions of these patients showed that they could copy very simple designs but were unable to represent perspective, that is, a cube. And drawing from memory showed characteristic disarticulation and piecemeal procedure (fig. 3). Designs were poorly copied. In some cases the patient was even slow and awkward in tying knots, often being satisfied with mere twists of the string. Furthermore, examinations with the Wechsler-Bellevue test gave results indicating an average or high intelligence level. Another striking note of similarity with cases of proven brain damage, and with cases of con-

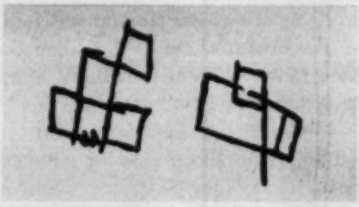

Fig. 3 (Goldberg, Marshall and Sims). Patient's attempt to draw a cross 21 days after operation. (Penfield and Hécaen.)

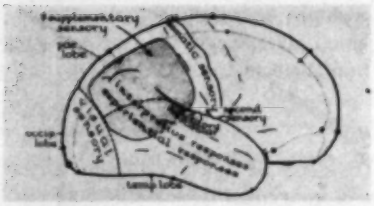

Fig. 4 (Goldberg, Marshall and Sims). The parietal-occipital area in which the predominant EEG abnormalities were found. (Penfield and Hécaen.)

genital dyslexia, is to be found in the electroencephalogram.

With the co-operation of the Baltimore County Schools a group of students from their remedial reading clinics were referred to us. These students were all of normal or superior intelligence but they were retarded two or more years in reading ability. General physical examinations were normal and there was little evidence of any abnormality in the ocular examinations. The eye examinations included complete and exhaustive muscle investigations, including muscle balance and fusional status. A group of patients of similar age and intelligence, but not retarded in reading, were included in our examinations so that they might serve as a control group.

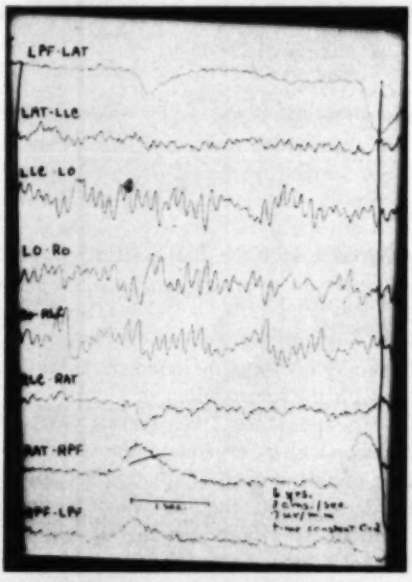

Fig. 5 (Goldberg, Marshall and Sims). Abnormal EEG of six-year-old child.

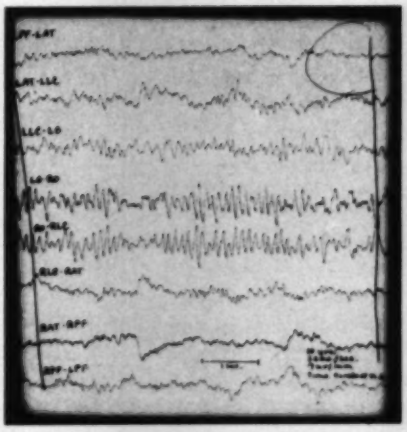

Fig. 6 (Goldberg, Marshall and Sims). Abnormal EEG of 11-year-old child.

Electroencephalographic interpretations were made by Dr. Curtis Marshall. The EEG's of a group of seven patients who had organic disease were scattered through the entire series. Twenty-five patients with reading retardation were examined and abnormalities were noted in 23 of 25 patients. There was an equal number of controls, and all but two cases of the control group were reported as normal.

The predominant abnormality in the EEG was in the parietal-occipital area and was characterized by general disorganization with asymmetry, abundant slow activity and occasional sharp waves, but no seizure discharges. This is exactly the finding in the electroencephalogram of the cases reported by Penfield and Hécaen (figs. 4, 5, 6, and 7).

Discussion

Children with reading retardation or congenital dyslexia were examined for evidence of subclinical brain damage. That such evidence was found is suggested by the results of the electroencephalogram and the psychologic tests involving perception.

The similarity of the EEG and the results of the psychologic tests in the patients with

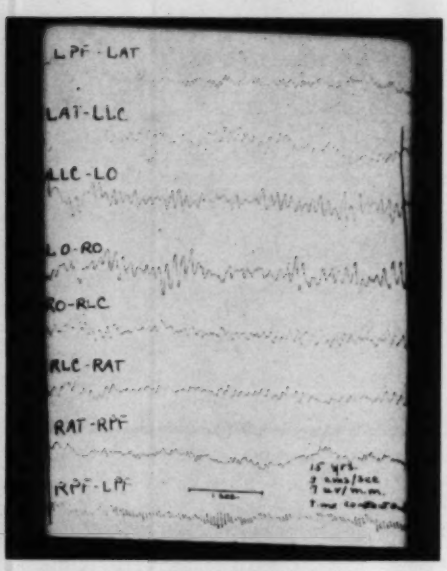

Fig. 7 (Goldberg, Marshall and Sims). Abnormal EEG of 15-year-old youth.

proven brain damage to some of those with congenital dyslexia would further suggest that brain damage is a factor in some of these cases.

Summary

1. Evidence of subclinical brain damage in cases of congenital dyslexia is suggested by EEG changes and psychologic visual-motor responses.

2. It is important for the educator to be aware of this group of subclinically brain damaged children so that remedial training can be instituted at an earlier age and "reading readiness" have even greater emphasis before the technique of reading is taught.

3. Educational, psychiatric and subclinical brain damage are proven etiologic factors of congenital dyslexia. Early recognition of these etiologic factors will be of assistance in choosing specific remedial therapy.

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CLINICAL RESULTS OF LIGHT COAGULATION THERAPY*

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The most important work presented to the ophthalmologic world in the past two decades is that of the use of light coagulation for the treatment of various eye conditions as developed by Meyer-Schwickerath at the University of Bonn in Germany. As was the case with the appreciation of Gonin's work 30 years ago, it has taken several years for ophthalmologists to realize the value and scope of this method of treating certain eye disorders. Admittedly, this type of treatment is still in its infancy, so that it will be a number of years before the limits of its use can be fully evaluated. However, even at this

* From the Division of Ophthalmology, Stanford University Medical School. Presented before the Pacific Coast Oto-Ophthalmological Society, Las Vegas, Nevada, May, 1959.

time, certain definite statements can be made as to its clinical value. The present paper is a brief presentation of our experience with this method of treatment, not only in our own hands but also from several periods of observation of the work at the University Eye Clinic at Bonn, Germany.

Retinal detachments come first to mind when light coagulation is mentioned, and rightly so, since it was for their prevention and treatment that this technique was first used. As will be pointed out in the latter portion of this paper, there are several other diseases in which it is equally or perhaps even more important.

In retinal detachment work, the use of light coagulation falls into two classifications: (1) its use in a prophylactic manner and (2) its use in helping to cure an existing detachment.

In prophylaxsis (table 1) one of the most important and dramatic aspects is the closing of retinal holes or tears found in the attached retina. Such definite holes may be found in the course of an ordinary eye examination, or they may be found in examining patients who have come in to the ophthalmologist complaining of flashes of light in an eye, or of spots like soot floating before an eye, or of a sudden haze developing before one eye, or several other such complaints or series of complaints. Furthermore, such "quiet holes" as just described, are, of course, often found in examining the fellow eye in a case of retinal detachment.

All such holes may be obliterated by means of light coagulation therapy. The easiest to treat are those located near or posterior to the equator but all holes, even those at the ora serrata, can be treated. The more anterior they are, however, the more difficult the technique and the greater the amount of skill required to seal them successfully.

TABLE 1

INDICATIONS FOR PROPHYLACTIC TREATMENT

1. Retinal tear without detachment
2. Degenerative areas in second eye
3. Cases of presenile cataract with degenerative retinal changes
4. Cases of cataract with previous retinal detachment surgery
5. Untreated peripheral retina after retinal detachment surgery

Although hints for easier use of the machine for light coagulation therapy will be listed at the end of this paper, at this point it seems pertinent to give suggestions for obliterating retinal holes. We have found it simplest first to put a very small barrage around the holes, avoiding all large retinal vessels. Then several coagulations can be put directly on the edges of the tear. These coagulations should look like those achieved by the use of very light diathermy. They should not coalesce but rather should look like "eggs in a carton." A row of such white spots is the ideal result. On the day after the coagulation, these coagulated points may look a little larger than at the time of treatment. After five or six days the white exudate should begin to disappear and pigment should be seen to appear. After about 10 days, all exudate is usually gone, although an increase in the amount of pigmentation present often continues for many days.

Another prophylactic use of light coagulation is to treat degenerated areas of the retina not infrequently seen in persons past middle age. Such areas show obliterated vessels or marked pigment atrophy with some pigment migration, or a combination of such findings.

Should all such areas be treated prophylactically? Undoubtedly not. Every experienced ophthalmologist has seen dozens of patients with such areas of degeneration who, over the years, needed nothing more than changes of glasses. The difficulty is making a clinical evaluation of each case. We feel that eyes with one or two such areas in patients with no complaints referable to such areas had best be left alone. In cases where slitlamp examination reveals a definite vitreoretinal adhesion, however, light coagulation therapy seems indicated. The same would hold true for a patient in whose other eye a frank retinal detachment had existed or does

exist; also one would probably be justified in treating these eyes if a member of the immediate family had developed a retinal detachment. However, we do not feel justified in recommending light coagulation for those patients who merely complain of occasional flashes of light unless definite pathologic changes are present.

Macular holes present another difficult clinical decision. Here again many patients show no further change after the initial eye examination. Years go by without a detachment developing. Undoubtedly, light coagulation therapy should be employed in those cases in which examination, especially with the slitlamp, suggests slight inward turning of the edge of a true hole, or even the faintest elevation of the retina about such a hole. If the vision has fallen to 20/200, an attached macular hole should probably be treated since vision would not be made worse by the coagulation. However, questionable holes in eyes with vision of 20/50 or 20/70 had best be watched for a considerable period of time before a decision to operate is made.

In retinal detachments, light coagulation can be used in less than 10 percent of new cases. Only those that settle out completely, and this means *completely*, are amenable to light coagulation. The slightest retinal elevation of even less than two diopters prevents the successful use of this therapy. In those cases that do settle out completely, the retinal holes can very satisfactorily be closed with light coagulation. As suggested for cases of retinal holes without detachment, a barrage (probably best a double barrage in these cases) should be placed around each retinal break, the edges of the holes should also be coagulated, and the barrage carried anteriorly to the ora serrata at several places.

In combination with, or supplementary to (table 2), some standard retinal detachment operations light coagulation therapy has an important role in the treatment of retinal detachments. Of most importance and greatest satisfaction to the ophthalmologist are the cases in which the retina has been reattached

TABLE 2

INDICATIONS FOR POSTOPERATIVE TREATMENT

1. Tear still open
2. Completion of electrodiathermy barrage
3. "Walling off" retained fluid
4. Treatment of other degenerative areas
5. Barrage central to a scleral resection

in the immediate postoperative period but in which ophthalmoscopy shows that the retinal hole (or holes) is still open and no operative exudative choroiditis is present in this region. How often the surgeon has wished he could apply just a little bit more diathermy at this point; to try to do this, however, usually proved to be an heroic operative procedure fraught with many complications. Now, with no more formidable procedure than a retrobulbar Novocaine injection, he can, with the light coagulation machine, easily produce new coagulations and new exudate at the right spot.

If sometimes the surgeon finds that a barrage of diathermy foci is weak at one point, he can easily add a few new coagulations or a whole new line of coagulation points to the existing foci. Thus, the light coagulation technique can prove of great help to every retinal detachment surgeon and, needless to say, these painless re-operations are greatly appreciated by the patient.

It should, however, be realized that although bloodless externally, this treatment is a serious operation. The light coagulation has coagulated and damaged not only retinal tissue but, more important, has obliterated and damaged capillaries and small venules and arterioles any of which may bleed, so some immediate postoperative rest seems indicated. Our routine is to use binocular bandages on the day of the light coagulation operation and then prescribing peephole glasses to be worn until all exudate has absorbed. Normal activity may be resumed in about two weeks.

When a full-blown retinal detachment is present which requires actual surgery and light coagulation is used only as a supple-

mentary procedure, postoperative care will be dictated by the progress of healing. In detachments which settle out so well preoperatively that light coagulation therapy is feasible, probably convalescence is somewhat shorter but, as these are cases in which a separation at the line of the pigment epithelium has occurred, it seems wise to err on the conservative side.

Another field for light coagulation therapy is in the treatment of von Hippel-Lindau disease. Its greatest advantage here is that, with proper technique, destructive intraocular hemorrhages are unknown. One must carefully avoid the large feeding vessels. Only the tumor should be treated. Depending on its size, two or three coagulations can be put directly on the tumor. In the succeeding days, small hemorrhages will appear on the surface of the tumor, which may take two to three weeks to disappear. At this time, or in about a month, a second treatment should be given, again avoiding the large vessels. After several weeks' wait, more treatment can be given. While this procedure is time consuming, it is safe.

Unlike diathermy, which can strike one of the large vessels and result in bad hemorrhage, it is possible to spare all large vessels, a feature of great value in monocular cases. As the tumor shrinks following these treatments, the enlarged vessels spontaneously diminish in size until they reach a normal size and distribution. Just as in treating retinal holes, it is possible to place all the light coagulation foci between the retinal vessels, a feat impossible with the diathermy technique.

Other retinal lesions successfully treated by this therapy are some cases of Eales' disease. The aborescent types are the most favorable. One should begin with coagulation of the smaller vessels and gradually work up to the largest. Cases of Leber's miliary aneurysms may also be treated, coagulating the aneurysm and its vessels if they are small in caliber.

In these two groups of cases, the amount of postoperative eye rest will have to be determined as the fundus picture develops; however, two to three weeks between treatments seems to be as short an interval as is advisable.

Diabetic retinopathy, unfortunately, reacts badly to this as well as to other types of treatment.

Marked success is usually obtained in treating small retinoblastomas with light coagulation. In our experience, this has been tried only in a remaining eye. Unfortunately, only small tumors, two- or three-disc diameters in size, are easily destroyed. As the retinoblastoma tumor contains little pigment, the heat is generated in the underlying choroid, so understandably, the tumor must be small. A ring of coagulations is first placed about the tumor which is then treated with several applications. After a week or two, more applications may be necessary and repeated treatments will depend on the fundus findings. Tumors that have recurred or resisted radiation seem very well suited to this type of therapy.

Small, malignant melanomas can also be successfully treated by light coagulation. As with retinoblastomas, a ring of coagulations is placed about the tumor and then the tumor is treated. Since there is much pigment present, smaller dosages of light are to be used. The interval between treatments can also be longer than with retinoblastoma. As yet, we have had no personal experience with melanomas.

Technique

The technique of light coagulation is fairly simple. The instrument, in principle a simple reflecting direct ophthalmoscope, is used accordingly. One should start with weak settings of the electric current and small diaphragm openings, increasing the settings until there is satisfactory coagulation. While the light is on, it is surprising how well one can see the coagulation appear in the fundus; so the time needed to develop coagulation can be accurately judged. More than two

seconds' exposure is probably not needed; since the choroidal circulation carries the heat away rapidly, longer exposures are not helpful.

One must have a maximally dilated pupil both for examining and for treatment. While not absolutely necessary, a retrobulbar injection of Novocaine is helpful in several ways. First, the eye is immobilized. This not only makes accurate focusing possible but also prevents the patients from suddenly looking at the light while it is on, thus badly damaging the macula. Secondly, retrobulbar Novocaine cuts down the patient's light sensitivity so that the treatment is tolerated well. Finally, if a little exophthalmos is produced, the periphery can be reached more easily. It may be necessary to turn the eye with forceps or a strabismus hook (best done by the assistant) and it may also be necessary to indent the sclera slightly to reach the ora serrata.

The cornea must be kept crystal clear. For this, irrigation with normal saline every 15 or 30 seconds is necessary. Lens opacities interfere markedly with the treatment and make it necessary to use much higher dosages than in eyes with clear lenses. However, in treating the peripheral retina, good coagulation can be achieved even with considerable nuclear lens opacity.

In marked ametropia (+10, or −10, or higher) contact glasses are needed to neutralize the refractive error. In such cases, a good contact-glass fluid seems to work better than normal saline.

Since Ophthaine or Dorsocaine, instilled once or twice, usually does not cause hazing of the cornea, it is a good local anesthetic to use. It reduces the patient's complaints about feeling the heat of the light, which is usually not painful. Also, the patients do not then complain of the eye feeling dry and irritated. Unless a retrobulbar injection is given, the light itself is quite disconcerting, to put it mildly, and so unbearable in some cases that the patients cannot hold their eyes still.

After the treatment, a bandage is applied. The cornea often shows a transient tendency to exfoliation of the epithelium, which the bandage seems to prevent. Within 24 hours the discomfort of this disappears.

Before closing, it might be well to point to some of the advantages and disadvantages of light coagulation therapy, as compared to the conservative use of diathermy.

The simplicity of the procedure is obvious and needs no further comment. Another factor in favor of light coagulation is that the areas of coagulation can be placed just where desired, which is not the case with diathermy. Therefore, hemorrhages into the vitreous cavity are rare. The ability to repeat the operation in a day or two in order to increase the coagulation effect is another great advantage.

The disadvantages are that light coagulation can be used only where the retina is completely attached, or practically completely reattached. Furthermore, with this technique no drainage of subretinal fluid is obtained.

A résumé of 224 cases treated by us is shown in Table 3. Several of the categories require no discussion. The one failure among

TABLE 3

LIGHT COAGULATION CASES*

Type	No.	Failed	Percent Failed
Postoperative	78	18	23.1
Hole without detachment	58	3	5.2
Prophylactic	27	0	0.0
Flattened with bedrest	15	6	40.0
Macular hole	11	0	0.0
Pupillotomy	8	5	62.5
von Hippel's disease	6	2	33.3
Retinoblastoma	5	2	40.0
Postoperative bleeding site	5	0	0.0
Coats' disease†	6	?	
Leber's aneurysms‡	5	?	
TOTAL	224		

* Additional cases have been added since the presentation of this paper. All cases have been followed for at least six months following the last treatment.

† Five cases are definitely better, one case is unchanged.

‡ The treated areas are all improved but in several cases new aneurysmal dilatations have appeared.

the cases with holes without detachment was in a doctor who had repeated vitreous hemorrhages. One large horseshoe tear was found and closed. Due to poor visibility, other retinal breaks apparently were not found and he developed a complete detachment of the retina.

The cases of prophylactic treatment of degenerated areas of retina, as well as the cataract cases treated prophylactically before operation, have been operated too recently (two to nine months) to allow any final conclusions.

In the detachments which settled with bedrest, two of the failures were due to faulty clinical judgment. In these, it was thought that the retina had settled sufficiently but, as was pointed out previously, practically complete settling is necessary. These failures bear out this point. The third failure, done at the beginning of the work, seemed to show sufficient coagulation at the time of treatment but detachment recurred within a few days of activity. Too little coagulation may have been the mistake.

Considering postoperative treatment, it is, of course, not possible to say how many cases would have improved if left alone. Judging by clinical experience, probably one half would not have been cured or would have relapsed. These include cases in which the holes were not completely closed, with some remaining detachment present, as well as cases with complete reattachment in which the holes were still open or where the delimiting barrage seemed incomplete or weak.

In two cases of von Hippel's disease shrinking is still taking place and the patients may need further treatment. The enlarged vessels have become normal in size and the "tumor" has practically disappeared.

The five cases of Leber's miliary aneurysms all improved in regard to the extent of the lesion, the number of aneurysms still visible, and in vision. How permanent these improvements will be remains to be seen.

In the cases of retinoblastoma, the failure was in a child who had the lesion in her second eye for many months before her family consented to treatment. Two courses of radiation combined with TEM failed and so did the light coagulation.

In the cases of persistent postoperative bleeders, the area suspected of being the bleeding point was treated with light coagulation and there has been no further bleeding for over six months in each case, which is longer than after any previous remission.

Only time will tell if all the cases listed in Table 1 as cures are permanent.

490 Post Street (2).

A CONTROLLED STUDY WITH TRICLOBISONIUM CHLORIDE*

IN EXTERNAL OCULAR INFECTION

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The development of strains of bacteria resistant to the commonly employed antibiotics is increasingly frustrating. In external ocular infection, as in all branches of medicine today, the treatment of disease with antibiotic and chemotherapeutic agents frequently results in failure and it becomes necessary to change drugs. Culture sensitivity studies have shown an increasing number of antibiotic resistant pathogens, particularly staphylococcus. As bacterial resistance to antibiotics develops, the search for new antibacterial agents must intensify and include the investigation of many newer bactericides.

* Triburon®, Hoffmann-La Roche Inc., Nutley, New Jersey.

The development of patient sensitization to the presently available antibiotics, both systemic and contact types, is a well-recognized problem and will undoubtedly increase with a more widespread use of antibiotics in medical practice. The desirability of limiting the use of antibiotics to systemic administration in the more severe medical problems makes more urgent the search for new antibacterial agents, which have topical effectiveness. The topical use of antibiotics which some day may be employed systemically in that patient is undesirable since it may lead to patient sensitization, and inability to use the drug with safety in the future.

Triclobisonium chloride, a bisquaternary diamine compound recently synthesized by Teitel and Goldberg of Hoffmann-La Roche, has been shown to possess "high bacteriostatic and moderate bactericidal activity in vitro" against a wide range of pathogens, including antibiotic-resistant staphylococci.[1] In vitro studies with both the disc plate sensitivity and with serial dilution techniques show triclobisonium chloride to be a very potent microbicide. The development of resistant strains has not thus far occurred in the laboratory.[1]

The structural formula of triclobisonium chloride, a stable, white, crystalline solid, readily soluble in water and ethanol, appears at the bottom of this page.

Buffered solutions of triclobisonium chloride in concentrations of one percent and over are irritating to mucous membranes, especially the conjunctiva. A 0.1-percent buffered aqueous solution of triclobisonium chloride was found to be nonirritating to the eye and was used in this study.[2]

The purpose of this investigation was to evaluate the therapeutic potential of triclobisonium chloride (0.1-percent buffered aqueous solution) in external ocular infections in laboratory animals and in patients.

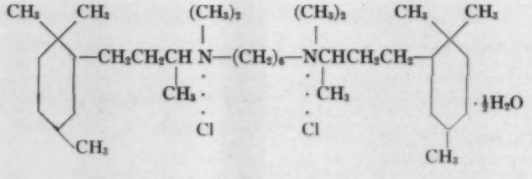
Animal studies

For these studies California and New Zealand albino rabbits were used. All rabbits were healthy and weighed approximately 2.0 kg. An experimental laboratory infection was produced by intracorneal injection of known dilutions of F.D.A. Staphylococcus aureus strain No. 209, containing between 4,000 and 100,000 viable organisms per ml. following the technique of Bellows.[3] A 25-gauge needle was used for the intracorneal injection and enough solution was injected to produce a four-mm. area of infiltration, manifested by corneal clouding.

The eyes of control animals progressed in the following manner: within eight hours, there was marked purulent conjunctivitis with injection of the episcleral vessels and marked iris congestion. A corneal ulcer developed approximately one to two mm. in diameter, which was whitish and necrotic. In 24 hours the size of the ulcer increased to four or five mm. and, in some cases, an early hypopyon developed. Within 48 hours the ulcer had expanded to between six and eight mm. and invariably there was hypopyon. A profuse purulent discharge and infection of the lacrimal system, evidenced by pus present in the nostril and maceration of the nares, was present.

Animals treated with triclobisonium chloride, after injection as already described, in a 0.1-percent solution, two drops in the conjunctival sac every hour, progressed as follows:

All eyes which received initial treatment within one hour after injection remained



clear, manifesting only a slight if any transitory conjunctivitis. Because of the consistently good results of the immediate treatment, it was decided to delay treatment beyond one hour after injection and allow the infection to become established. When treatment was delayed two hours, a small ulcer, one to two mm. developed but did not progress. Eyes in which treatment was delayed three to four hours after injection developed correspondingly larger ulcers, two to four mm., which also did not progress. It should be noted that the number of organisms used in these experiments was in many instances much higher than those employed by Bellows in a previous study using a similar technique.

Anterior chamber drug levels

In this study three rabbits were used. Five eyes were bathed with triclobisonium chloride (0.1-percent solution) every 10 minutes for four doses. One untreated eye was used as a control. Using a 25-gauge needle the anterior chambers were punctured with a syringe wetted with heparin. At 15 minutes 0.2 cc. of aqueous humor was withdrawn from one eye; at 30 minutes a second sample; and again at 60, 120, and 240 minutes respectively. The same procedure was used on the control eye. This aqueous humor was dropped into a series of 10 tubes of known dilution of staphylococcus. No inhibition of growth appeared in any of the tubes.

Six more eyes were then totally debrided of corneal epithelium and similarly bathed with triclobisonium chloride at 10-minute intervals. Anterior chamber punctures were carried out by the same technique and at the same intervals as before. Serial dilution study was performed in the same manner. Inhibition of growth was evident in the 15-minute sample of aqueous humor and continued to show high concentration of triclobisonium chloride through the four hours. There was no inhibition of growth by the aqueous humor of the control eye. Computation revealed that concentration of triclobisonium chloride in the rabbit aqueous humor at one hour after the corneal bath was 40 μg. per ml.

Corneal re-epithelization

Six eyes in three rabbits were totally denuded of corneal epithelium. The right eye in each rabbit was treated with one drop of 0.1-percent triclobisonium chloride every hour. The left eye was untreated. All corneas were stained with fluorescein at eight, 24, and 48 hours in order to note the rate of re-epithelization. There was no significant difference in the rate of re-epithelization of the corneas in either group, and healing in all cases was complete within 48 hours.

Clinical studies

One hundred and twenty consecutive cases of external ocular infection at the clinic* comprised this study. These cases, diagnosed by clinical examination, consisted of acute and chronic conjunctivitis, corneal ulcer and hordeola. Bacteriologic studies preceded all treatment and consisted of initial gram and Giemsa staining, cultures, and sensitivity studies.

Treatment consisted of one drop of 0.1-percent buffered aqueous solution of triclobisonium chloride every three to four hours. Patients were seen daily and repeat cultures were taken on each successive day throughout treatment. The patients who evidenced no significant improvement after 48 hours were regarded as failures and other therapy was instituted. All eyes showing improvement were continued on this therapy until a clinical cure was obtained, after which treatment was discontinued. Patients were re-examined bacteriologically one week after treatment was stopped.

All bottles of medication were returned after treatment was discontinued and were cultured for contamination.

The following criteria of the effectiveness of the medication were used: *Cured:* clinical

* United Hospitals of Newark, Newark Eye and Ear Unit, Newark, New Jersey.

TABLE 1

STUDIES WITH 0.1-PERCENT TRIBURON OPHTHALMIC SOLUTION AT NEWARK EYE AND EAR HOSPITAL

Organisms	Diagnosis			Results		
	Acute Conjunctivitis	Chronic Conjunctivitis	Miscellaneous*	% Cured	% Improved	% Failure
Staphylococcus albus	23	10	2	68.6	25.7	5.7
Staphylococcus aureus	12	7	11	76.7	23.3	0.0
Staphylococcus epidermidis	1	6	3	60.0	20.0	20.0
Streptococcus pyogenes	4	3	3	60.0	40.0	0.0
Proteus vulgaris	4	0	2	66.7	33.3	0.0
Fungus	0	0	2	50.0	0.0	50.0
Bacillus subtilis	7	1	2	60.0	30.0	10.0
Micrococcus tetragenus	0	1	0	100.0	0.0	0.0
Moraxella Axenfeld	6	2	1	55.6	33.3	11.1
Escherichia coli	1	2	0	66.7	33.3	0.0
Koch—Weeks	1	2	1	100.0	0.0	0.0
TOTAL†	59	34	27	66.6	27.8	5.6

* Miscellaneous cases include hordeolum, blepharitis, and corneal ulcers.

† Not included in the total cases evaluated are 20 percent of patients treated who did not return or could not be treated beyond the initial day.

cure and bacteriologically negative one week after treatment was stopped. *Improved:* clinical cure but sparse bacterial growth one week after cessation of therapy. *Failure:* patients showing no improvement clinically within 48 hours who were changed to other therapy. Table 1 summarizes the clinical and bacteriologic findings in the 120 cases.

These percentages do not include 20 percent of all cases for which there was insufficient follow-up. The bacteriologic spread in the cases not followed closely approximated the over-all picture.

Clinical improvement in most cases was evident in three to four days. The time of clinical cure ranged from two to 10 days with an average of five days from start of treatment.

DISCUSSION

From the bacteriologic survey, it is apparent that staphylococcus was the most common pathogen in external ocular infection in our study (65 percent). This differs markedly from previous bacteriologic studies[4-7] carried out in the pre-antibiotic era and suggests that antibiotics are changing the bacteriology of ocular infection. The low percentage of Morax-Axenfeld and Koch-Weeks infections and absence of pneumococcus are remarkable.

A 0.1-percent buffered aqueous solution of triclobisonium chloride produced no deleterious effects and was not irritating to the eye. There developed a single case of contact-type sensitivity which showed an eczematous reaction of the lids; this responded to local steroid therapy.

The bottles containing the medication were returned by the patients after conclusion of therapy. The remaining solution or empty bottles were cultured. Over 98 percent of all bottles were sterile on culture.

Not included in Table 1 is a series of 16 white clinically clean preoperative eyes cultured one week before surgery and treated with triclobisonium chloride four times a day and smeared and cultured again the day before surgery. These eyes were bacteriologically negative after treatment.

SUMMARY AND CONCLUSION

Triclobisonium chloride was used in treatment of experimentally produced staphylococcal corneal ulcer and was found to be effective in the prevention and treatment of these ulcers. The medication did not adversely affect the rate of corneal re-epitheli-

zation, nor did it penetrate the intact cornea, but was found in significant levels in the aqueous humor when the cornea was abraded.

Triclobisonium chloride was found to be effective in 94 percent of all ocular infections treated in the clinical study. It was generally nonirritating with no apparent side-effects.

It is concluded from our experience that triclobisonium chloride is a useful drug in the prevention and control of external ocular infection.

180 Clinton Avenue (5).

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CLINICAL AND EXPERIMENTAL CONSIDERATION OF CYCLOELECTROLYSIS AND CYCLODIATHERMY*

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It is evident from a study of the literature, that ophthalmologists have appreciated the need for some operation which could diminish the secretion of aqueous. Most of the methods employed to accomplish this are included in Table 1.

The writing of this paper was motivated by the desire to determine whether, with improved knowledge through wider operative experience in animals and humans involving these different currents, the postoperative results of cyclodiathermy and cycloelectrolysis would be the same as in our previous studies. It seemed particularly important to know whether atrophy of the eyeball was still a serious complication of cyclodiathermy as we had previously reported.[12,13]

To determine the effect of these operations on human glaucomatous eyes, 1,600 questionnaires† were sent to members of the French Ophthalmological Society and of the American Ophthalmological Society.

It has been definitely established clinically and experimentally, that there is a great

* From the Department of Research, New York Association for the Blind and the Department of Ophthalmology, New York University Post-Graduate School of Medicine. Read in part before the XVIII International Congress of Ophthalmology, Brussels, Belgium, September, 1958. Aided by a grant from The Ophthalmological Foundation Inc.

† We express our deep appreciation to all ophthalmologists who responded to the questionnaire. The following ophthalmologists or clinics have generously furnished case histories for this statistical study. Glaucoma Clinic, University of California; University of Michigan (Drs. Landis Fralick, Falls and Henderson); Drs. Rychener, Arnold, Weve, Foster, Bishay, Evereux, Lovery, Miller, Meyers, Hogan, Arkin, Hermanns, Dekking, Fau, Castroviejo, Dunnington, Cavka, Borley, Lepard, Benner, Appleman, Hartmann, Hays, Smith, Eerden, Miller, Barraquer, Lefferstra, Calamandrel, Hughes, Dupont, Dollfus, Offret, Coppez, Vydosky, Hudson, Dienstbier, Delthil, Franschetti; New York Eye and Ear Infirmary and Manhattan Eye and Ear Infirmary.

TABLE 1

SURVEY OF LITERATURE

Year	Author	Operation Employed
1921	Shahan and Post[1]	Thermophore
1924	Verhoeff[2]	Cyclectomy
1925	Curran[3]	Cauterization of sclera, subconjunctivally
1932	Weve[4]	Nonpenetrating cyclodiathermy
1937	Vogt[5]	Penetrating cyclodiathermy
1944	Guerry[6]	Angiodiathermy of the long posterior ciliary arteries
1944	Cavka[7]	Anterior and posterior nonpenetrating cyclodiathermy combined with cyclodialysis
1946	Berens[8]	Cycloelectrolysis (anterior)
1947	Bietti[9]	Carbon dioxide snow
1947	Schreck[10]	Ciliocycloanolysis
1949	Weekers[11]	Retrociliary diathermy
1949	Berens[12]	Cycloelectrolysis (posterior)
1954	Berens[13]	Circumcorneal cycloelectrolysis
1956	Weekers[14]	Ischemia of ciliary body

tendency for the tension of the eye gradually to return to the preoperative mean after cyclodiathermy and cycloelectrolysis. It is believed, therefore, that to obtain more valid statistics, only eyes observed for a minimum period of one year, should be included in the cases reported. However, in some instances the data obtained made it impossible to isolate those cases observed postoperatively for less than one year.

A resumé of the replies received are tabulated in Table 2.

Ophthalmologists who have abandoned cyclodiathermy because of poor results or because of the serious complications encountered postoperatively include: Drs. Fielta, Foster, Pischel, Arganarez, Bruckner, McGavic, Harrington, Swan, Hoorens, Vail, Goar, Sakic and Lloyd. Furthermore, the literature contains numerous articles reporting serious complications ophthalmologists* have encountered following the use of cyclodiathermy.

In a careful study of all the records of cyclodiathermy and cycloelectrolysis submitted, it is evident that more ophthalmologists are now employing nonpenetrating retrociliary diathermy than anterior cyclodiathermy. Of the 2,574 cases tabulated, 700 were nonpenetrating retrociliary cyclodiathermy, 570 were penetrating retrociliary cyclodiathermy, 174 were nonpenetrating anterior cyclodiathermy, 320 were penetrating anterior cyclodiathermy and 324 were anterior and posterior nonpenetrating cyclodiathermy combined with cyclodialysis (Čavka technique). Of the 426 cycloelectrolysis operations tabulated, only 38 were retrociliary.

The postoperative results of a series of 174 eyes following nonpenetrating anterior cyclodiathermy, observed for from one to eight years, are tabulated in Table 3.

DISCUSSION OF TABLE 3

Nonpenetrating anterior cyclodiathermy was used as a primary procedure in 73 percent of the 174 eyes observed for from one to eight years (the majority however, were followed for from one to two years). Additional antiglaucoma surgery was performed

TABLE 2

RESULTS OF QUESTIONNAIRE

	No. of Ophthalmologists
Insufficient experience	39
Do not employ techniques	36
Abandoned cyclodiathermy because of poor results or serious complications	14
Incomplete data (not used in survey)	23
Case histories used	44

* Streiff, Thomas, Schreck, deRoetth, Bietti, Scheie, Woods, Swan, Arganarez, Lachman, Berens, Bodian, van Heuven and Covel.

TABLE 3

POSTOPERATIVE RESULTS OF NONPENETRATING ANTERIOR CYCLODIATHERMY IN 174 EYES OBSERVED FOR FROM ONE TO EIGHT YEARS

Type of Glaucoma A. Primary surgery B. Additional surgery (percent)	No. of Eyes	Tension* (percent)					Enucleation or Evisceration (percent)	Visual Fields† (percent)		
		1	2	3	4	5		1	2	3
Chronic simple-open A. 66 B. 46	61	2 29	27	29	2	40	0	7 28	21	72
Chronic simple-closed A. 62 B. 45	21	13 37	24	13	0	50	0	0 54	54	46
Acute A. 25 B. 75	3	33 33	0	0	0	33	33	0	0	0
Aphakia A. 87.5 B. 36	30	7 28	21	34	4	17	17	0 34	34	66
Uveitis A. 100 B. 37.5	26	19 23	4	39	4	34	0	0 60	60	40
Hemorrhagic A. 100 B. 30	18	6 30	24	16	6	24	24	0 24	24	75
Buphthalmos	4	0	0	75	0	0	25	0	0	0
Secondary-miscellaneous A. 73 B. 36	11	28 28	0	18	0	36	18	0	0	100
MEAN TOTAL A. 73 B. 41	174	10 29	19	28	3	33	7	7 36	29	64

* Tension: 1. Controlled without miotics (under 25 mm. Hg Schiøtz). 2. With miotics. 3. Decreased (over 25 to 35 mm. Hg). 4. Hypotonic. 5. Uncontrolled.
† Fields: 1. Improved. 2. Unchanged. 3. Decreased or lost.

in 41 percent of the eyes, but tension remained uncontrolled in 33 percent of the 174 eyes.

Tension was controlled without miotics in 10 percent, and with miotics in 19 percent for a total of 29 percent controlled under 25 mm. Hg (Schiøtz). Tension was decreased in 28 percent (above 25 mm. Hg to 35 mm. Hg) and three percent of the eyes became hypotonic. Seven percent of the 174 eyes were either enucleated or eviscerated. Visual fields were improved in seven percent, unchanged in 29 percent and were decreased or lost in 64 percent of the eyes.

The postoperative results of a series of 320 eyes following penetrating anterior cyclodiathermy, observed for from three months to four years, are tabulated in Table 4.

DISCUSSION OF TABLE 4

Although the request was made to submit cases observed for a minimum period of one year postoperatively, over one third of the 320 eyes tabulated in Table 4, were observed under one year. Penetrating anterior cyclodiathermy was used as a primary procedure in 92 percent of the eyes, and although additional surgery was performed in over half of the cases, tension remained uncontrolled in 27 percent of the 320 eyes. Tension was controlled in eight percent without miotics

TABLE 4

POSTOPERATIVE RESULTS OF PENETRATING ANTERIOR CYCLODIATHERMY IN 320 EYES OBSERVED FOR FROM THREE MONTHS TO FOUR YEARS

Type of Glaucoma A. Primary operation B. Additional surgery (percent)	No. of Eyes	Tension* (percent)					Enucleation or Evisceration (percent)	Visual Fields† (percent)		
		1	2	3	4	5		1	2	3
Chronic simple-open A. 79 B. 69	80	14	37 51	19	5	23	2	13	36 49	51
Chronic simple-closed A. 82 B. 27	115	5	38 43	27	4	22	4	12	49 61	39
Acute A. 85 B. 35	20	0	30 30	25	15	25	5	12	19 31	69
Aphakia A. 91 B. 36	28	11	35 46	25	3+	22	3+	0	25 25	75
Uveitis A. 86 B. 43	29	10	14 24	31	7	31	7	0	34 34	66
Hemorrhagic A. 85 B. 55	11	0	18 18	18	0	55	9	0	25 25	75
Diabetic Rubeosis Iridis A. 87 B. 52	8	37	0 37	37+	0	25	0	0	0	100
Secondary Miscellaneous A. 64 B. 88	29	3	20 23	14	7	42	14	0	63 63	37
MEAN TOTAL A. 92 B. 51	320	8	31 39	23	7	27	4	5	51 56	44

* Tension: 1. Controlled without miotics (under 25 mm. Hg Schiøtz). 2. With miotics. 3. Tension decreased between 25–35 mm. Hg. 4. Hypotonic. 5. Uncontrolled.
† Visual fields: 1—Improved; 2—unchanged; 3—decreased or lost.

and in 31 percent with miotics (under 25 mm. Hg Schiøtz). Tension was reduced in 23 percent (between 25 and 35 mm. Hg), seven percent of the eyes became hypotonic and four percent of the 320 eyes were enucleated or eviscerated.

Visual fields were improved in five percent, remained unchanged in 51 percent and were decreased or lost in 44 percent of the eyes.

The postoperative results of 700 eyes following nonpenetrating retrociliary diathermy, observed for from two months to 14 years, are tabulated in Table 5.

DISCUSSION OF TABLE 5

In this significant series of 700 eyes observed for from two months to 14 years, following nonpenetrating retrociliary diathermy, which was employed as a primary procedure in 77 percent of the eyes, approximately 30 percent were observed under one year and 45 percent were followed for from one to two years. Tension remained uncontrolled in 24 percent of the 700 eyes in spite of the fact that additional surgery was performed on 43 percent of the eyes. Tension was controlled without miotics (under 25 mm. Hg Schiøtz) in 18 percent,

TABLE 5

POSTOPERATIVE RESULTS OF NONPENETRATING RETROCILIARY CYCLODIATHERMY IN 700 EYES OBSERVED FOR FROM TWO MONTHS TO FOURTEEN YEARS

Type of Glaucoma A. Primary operation B. Additional surgery (percent)	No. of Eyes	Tension* (percent)					Enucleation or Evisceration (percent)	Visual Fields† (percent)		
		1	2	3	4	5		1	2	3
Chronic simple-open A. 92 B. 33	138	13	35 48	21	6	22	3	6	35 41	59
Chronic simple-closed A. 84 B. 56	92	18	28 46	15	5	22	2	3	27 30	70
Acute A. 71 B. 50	31	10	26 36	36	6	19	3	0	34 34	66
Aphakia A. 70 B. 54	111	10	25 35	24	10	24	7	1	39 40	60
Uveitis A. 97 B. 50	92	23	23 46	14	12	21	7	4	17 21	79
Buphthalmos A. 45 B. 23	62	18	22 40	16	6	30	8	0	0	0
Juvenile & congenital A. 62 B. 38	17	17	41 58	6	12	24	0	0	0	0
Aniridia A. 67 B. 33	6	50	33 83	0	17	0	0	0	0	0
Microphthalmos (observed—2 mo.)	2	1	1							
Megalocornea	4	0	0	50	0	50	0	0	0	0
Hemorrhagic A. 92 B. 48	50	12	14 26	6	4	44	20	0	25 25	75
Secondary miscellaneous A. 76 B. 57	85	30	22 52	12	15	19	2	8	15 23	76
Absolute A. 91 B. 27	13	0	15 15	15	0	40	30	0	0	0
MEAN TOTAL A. 77 B. 43	700	18	27 45	17	8	24	6	4	30 34	66

* Tension: 1. Controlled without miotics (under 25 mm. Hg Schiøtz). 2. With miotics. 3. Tension reduced (over 25 to 35 mm. Hg). 4. Hypotonic. 5. Uncontrolled.
† Visual fields: 1. Improved. 2. Unchanged. 3. Decreased or lost.

and with miotics in 27 percent for a total of 45 percent of the eyes controlled. Tension was reduced between 25 and 35 mm. Hg in 17 percent and eight percent of the eyes became hypotonic, and six percent were enucleated or eviscerated.

TABLE 6

POSTOPERATIVE RESULTS OF PENETRATING RETROCILIARY CYCLODIATHERMY IN 507 EYES OBSERVED FOR FROM ONE MONTH TO SIX YEARS

Type of Glaucoma A. Primary operation B. Additional surgery (percent)	No. of Eyes	Tension* (percent)					Enucleation or Evisceration (percent)	Visual Fields† (percent)		
		1	2	3	4	5		1	2	3
Chronic simple-open A. 91 B. 59	164	8 37	29	45	4	12	2	4 40	36	60
Chronic simple-closed A. 50 B. 77	130	14 55	41	29	2	12	2	1 61	60	39
Acute A. 82 B. 64	52	2 30	28	38	2	28	2	5 35	30	65
Aphakia A. 84 B. 60	80	21 48	27	21	10	13	8	0 43	43	57
Uveitis A. 67 B. 60	57	28 45	17	33	4	10	8	13 48	35	52
Hemorrhagic A. 75 B. 25	41	31 43	12	12	5	22	18	0 8	8	92
Diabetic rubeosis irides A. 92 B. 75	22	9 23	14	5	14	36	22*	0 39	39	61
Congenital A. 64 B. 40	11	0 9	9	18	18	46	9	0	0	0
MEAN TOTAL A. 77 B. 52	570	15 44	29	30	4	17	5	4 46	42	54

* Tension: 1. Controlled without miotics (under 25 mm. Hg Schiøtz). 2. With miotics. 3. Decreased (over 25 mm. Hg to 35 mm. Hg). 4. Hypotonic. 5. Uncontrolled.
† Visual fields: 1. Improved. 2. Unchanged. 3. Decreased or lost.

Visual fields were improved in four percent, remained unchanged in 30 percent and were reduced or lost in 66 percent of the eyes.

Of especial interest and included in this series of 700 eyes are the 154 cases of nonpenetrating retrociliary diathermy submitted by Weve, observed for from one to 14 years. In Weve's series of cases, 39 percent of the 154 eyes were controlled with and without miotics, following additional surgery in 39 percent of the eyes. A high incidence of atrophy and phthisis bulbi, which is discussed under postoperative complications, was reported in this series of eyes.

The postoperative results of 570 eyes following penetrating retrociliary cyclodiathermy, observed for from one month to six years, are tabulated in Table 6.

DISCUSSION OF TABLE 6

Penetrating retrociliary cyclodiathermy was performed as a primary procedure in 77 percent of the 570 eyes and 17 percent of the eyes remained uncontrolled in spite of additional surgery required in over half of the eyes. Tension was controlled in 15 percent of the eyes without miotics (under 25

mm. Hg Schiøtz) and in 29 percent with miotics for a total of 44 percent of the eyes controlled. In this series of 570 eyes, are included 107 case histories submitted by Barraquer, which were observed for from one to 12 months following penetrating retrociliary diathermy. In Barraquer's series of cases, tension was controlled in only 26 percent of the eyes (with and without miotics).

The tension in 30 percent of the 570 eyes was reduced between 25 and 35 mm. Hg (Schiøtz); four percent of the eyes became hypotonic and five percent were enucleated.

Visual fields were improved in four percent, remained unchanged in 42 percent and were decreased or lost in 54 percent of the eyes.

Cyclodialysis was combined with cyclodiathermy in several of the operations reported but the number was insufficient to evaluate. However, Čavka[7] who combines anterior and posterior nonpenetrating cyclodiathermy with cyclodialysis submitted the postoperative results in 324 eyes observed for from one to seven years, which are tabulated in Table 7.

Discussion of Table 7

The operation was used as a primary procedure in 324 eyes and tension was controlled under 25 mm. Hg (Schiøtz) in 38 percent without miotics and with miotics in 35 percent for a total of 73 percent of the 324 eyes.

Additional surgery was required in only six percent of these eyes, which were observed for from one to seven years postoperatively. Tension was decreased (between 25 to 35 mm. Hg) in six percent of the eyes and 21 percent of the 324 eyes became hypotonic. Visual fields were improved in 30 percent, unchanged in 65 percent and reduced or lost in five percent of the eyes.

The excellent results reported by Čavka merit further study of this technique, which consists of applying a 1.5 mm. ball electrode to the sclera after reflecting a conjunctival flap, using 50 ma. of current for one second. The diathermy applications are made in three horizontal and four vertical lines from 2.5 to 8.0 mm. from the corneal limbus.

A scleral incision is made 2.0 mm. from the limbus and cyclodialysis performed from the 11:30- to 2:30-o'clock positions.

TABLE 7

POSTOPERATIVE RESULTS OF ANTERIOR AND POSTERIOR NONPENETRATING CYCLODIATHERMY WITH CYCLODIALYSIS IN 324 EYES OBSERVED FOR FROM ONE TO SEVEN YEARS

Type of Glaucoma Primary operation in all B. Additional surgery (percent)	No. of Eyes	Tension* (percent)					Visual Fields† (percent)		
		1	2	3	4	5	1	2	3
Chronic simple-open B. 6	167	35 74	39	4	22	0	35 95	60	5
Chronic simple-closed B. 9	61	39 70	31	7	23	0	51 91	40	9
Acute B. None	7	57 100	43	0	0	0	0	0	0
Aphakia B. 6	84	38 71	33	8	21	0	0	0	0
Hydrophthalmos B. None	5	60 80	20	20	0	0	0	0	0
Mean total B. 6	324	38 73	35	6	21		30 95	65	5

* Tension: 1. Controlled without miotics (under 25 mm. Hg Schiøtz). 2. With miotics. 3. Tension reduced (over 25 to 35 mm. Hg). 4. Hypotonic. 5. Uncontrolled.

† Visual fields: 1. Improved. 2. Unchanged. 3. Decreased or lost.

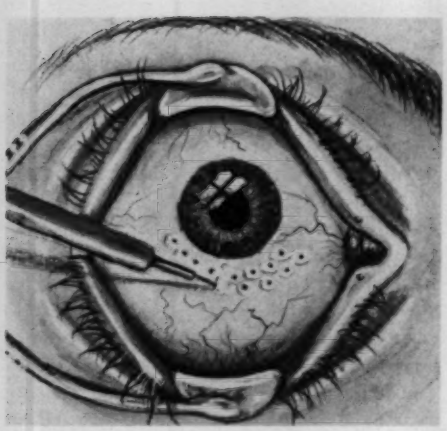

Fig. 1 (Berens and Sheppard). Anterior cycloelectrolysis. Galvanic current applications (cathode) are made between 2.0 and 4.0 mm. from the corneal limbus.

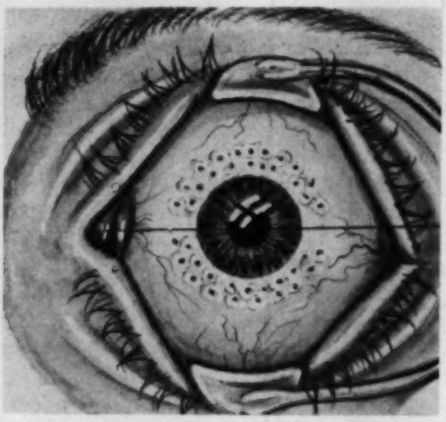

Fig. 2 (Berens and Sheppard). In circumcorneal cycloelectrolysis, the long posterior ciliary arteries are avoided. Applications are made between 2.0 and 4.0 mm. from the cornea.

Cycloelectrolysis

The mode of action of cycloelectrolysis differs from cyclodiathermy in that in cycloelectrolysis there is a controlled chemical (sodium hydroxide) destruction of the ciliary body and ciliary nerves produced by the negative (cathode) galvanic current, whereas in cyclodiathermy, atrophy of the ciliary body is produced by heat and there is greater shrinkage and destruction of the sclera.

Techique of cycloelectrolysis

The positive pole pad attached to a galvanic battery (with a potential of at least 22.5 volts and a milliampere scale large enough to show small variations between 0 and 10 ma.) is placed to the patient's shoulder, covered by electrolytic jelly to create good contact.

A special straight platinum needle 2.0 mm. in length and 0.18 mm. in diameter is applied at the lower half of the eyeball through the conjunctiva, applying from 20 to 60 punctures between 2.0 and 4.0 mm. from the limbus for anterior applications (fig. 1). The punctures may be repeated in the upper half of the eyeball after three weeks. In circumcorneal cycloelectrolysis[15] the applications are placed 2.0 and 4.0 mm. from the limbus, avoiding the long posterior ciliary arteries (fig. 2).

In retrociliary cycloelectrolysis the punctures are applied from 6.0 to 7.0 mm. from the limbus between the recti insertions, avoiding the long posterior ciliary arteries (fig. 3). Five milliamperes of negative pole galvanic current are applied for five seconds for each puncture. Under local anesthesia three ma. of current may be used for 10 seconds.

If the tension remains high immediately following surgery, from 0.5 to 1.0 cc. of aqueous may be slowly aspirated from the anterior chamber (fig. 4).

Cyclodialysis may be combined with cycloelectrolysis in some cases.

Postoperatively, a solution of atropine (one percent) is instilled and 1:3,000 metaphen ointment and a monocular dressing are applied. The head and torso should be elevated but rest in bed is unnecessary. Scopolamine hydrobromide (0.25 percent) or additional instillations of atropine (one percent) may be helpful in lessening congestion and in producing mild dilatation of the pupil.

Cortisone and iced compresses reduce inflammation but Sheppard[16] cautions against the immediate use of cortisone after cycloelectrolysis or cyclodiathermy, or if cortisone is necessary, to administer antibiotics simultaneously.

The postoperative results of anterior cycloelectrolysis in 388 eyes observed for from one to 12 years, are tabulated in Table 8.

Discussion of Table 8

Tension was controlled (under 25 mm. Hg Schiøtz) in 29 percent without miotics and in 36 percent with miotics in 388 eyes observed for from one to 12 years following anterior cycloelectrolysis. The majority of these cases were followed for from three to six years. The operation was used as a primary procedure in only 47 percent of the eyes. Additional surgery was required in 26 percent of the 388 eyes. Tension was reduced to between 25 to 35 mm. Hg in 18 percent, seven percent became hypotonic and four percent of the 388 eyes were enucleated. Visual fields were improved in 32 percent, remained unchanged in 27 percent and were reduced or lost in 41 percent of the eyes.

The gradual lessening of effectiveness of cycloelectrolysis was demonstrated in a previous report,[13] in a series of 239 eyes observed for from two to nine years where tension was controlled in 65 percent following additional surgery in 19 percent of this series of eyes. Of the total of 239 eyes, 199 eyes were observed for from two to six years with tension controlled in 67 percent, following additional surgery in 14 percent of the eyes. The remaining 40 eyes were observed for from seven to nine years with tension controlled in 60 percent following additional surgery in 25 percent of the eyes, indicating a loss of seven percent of eyes controlled within a three-year period with an increase of nine percent of the eyes that required reoperation.

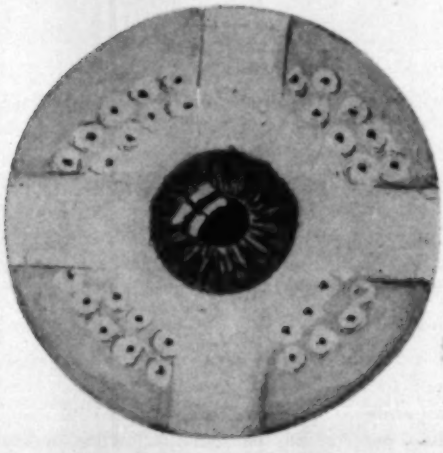

Fig. 3 (Berens and Sheppard). Retrociliary cycloelectrolysis. Applications are placed from 6.0 to 7.0 mm. from the limbus between the recti muscles.

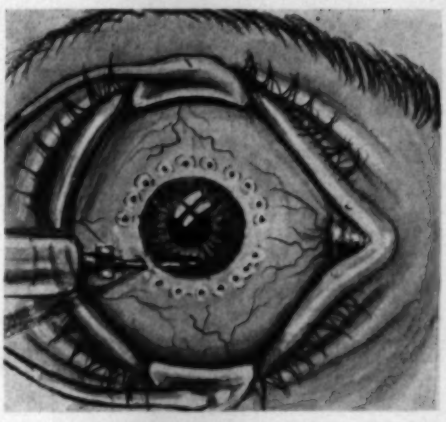

Fig. 4 (Berens and Sheppard). From 0.5 to 1.0 cc. of aqueous is aspirated from the anterior chamber if tension remains high.

The loss of effectiveness was somewhat lower with more surgery required to control tension following anterior cyclodiathermy than following cycloelectrolysis. In a study of 264 eyes following cyclodiathermy observed for from one to 14 years,[13] tension was controlled in 28 percent following additional surgery in 31 percent of the eyes. Of these, 114 eyes were observed for from one to six years with tension controlled in 35 percent, but a third of the eyes required one or more additional operations. The remain-

TABLE 8

POSTOPERATIVE RESULTS OF ANTERIOR CYCLOELECTROLYSIS IN 388 EYES OBSERVED FOR FROM ONE TO TWELVE YEARS

Type of Glaucoma A. Primary operation B. Additional surgery (percent)	No. of Eyes	Tension* (percent)					Enucleation or Evisceration (percent)	Visual Fields† (percent)		
		1	2	3	4	5		1	2	3
Chronic simple-open A. 19 B. 15	120	36 75	39	16	5	4	0	31 61	30	39
Chronic simple-closed A. 25 B. 12	32	27 69	42	19	4	8	0	14 57	43	43
Acute A. 41 B. 22	19	29 64	35	24	0	6	6	36 64	28	36
Aphakia A. 53 B. 21	62	19 53	34	15	12	12	8	30 39	9	61
Uveitis A. 59 B. 10	39	39 66	27	14	6	11	3	54 75	21	24
Hemorrhagic A. 62 B. 24	19	15 57	42	16	11	11	6	17 67	50	33
Diabetic rubeosis irides A. 73 B. 35	6	17 34	17	32	0	17	17	33 66	33	33
Thrombosis central vein A. 50 B. 50	6	33 50	17	33	0	17	0	0	0	0
Buphthalmos A. 25 B. 27	21	24 63	39	28	0	9	0	0	0	0
Secondary-miscellaneous A. 32 B. 38	35	24 52	28	24	12	6	6	0	100	0
Absolute A. 90 B. 30	29	20 48	28	24	12	0	16	0	0	0
MEAN TOTAL A. 47 B. 26	388	29 65	36	18	7	6	4	32 59	27	41

* Tension: 1. Controlled without miotics (under 35 mm. Hg Schiøtz). 2. With miotics. 3. Reduced (25 to 35 mm. Hg). 4. Hypotonic. 5. Uncontrolled.

† Visual fields: 1. Improved. 2. Unchanged. 3. Decreased or lost.

ing 150 eyes in this series were observed for from seven to 14 years with tension controlled in only 22 percent, indicating a loss of effectiveness in 13 percent of the eyes over a period of eight years. Atrophy of the globe was observed in 11 percent of the 264 eyes following anterior cyclodiathermy and 6.5 percent of 114 eyes observed for from one to five years following retrociliary diathermy as compared with atrophy in only one percent of the eyes following cycloelectrolysis.

The postoperative results of 38 eyes following retrociliary cycloelectrolysis observed

TABLE 9

POSTOPERATIVE RESULTS IN 38 EYES FOLLOWING RETROCILIARY CYCLOELECTROLYSIS OBSERVED FOR FROM TWO TO FOUR YEARS

Type of Glaucoma A. Primary operation B. Additional surgery (percent)	No. of Eyes	Tension* (percent)					Enucleation or Evisceration (percent)	Visual Fields† (percent)		
		1	2	3	4	5		1	2	3
Chronic simple-open A. 63 B. 25	10	10 50	40	20	20	0	10	17 67	50	33
Chronic simple-closed A. 75 B. 40	6	60 80	20	20	0	0	0	0 75	75	25
Acute	1			1						
Aphakia A. 75 B. 50	8	25 37	12	38	0	0	0	0	0	0
Hemorrhagic A. 75 B. 75	5	0 40	40	40	20	0	0	0	0	0
Secondary-miscellaneous A. 87 B. 25	8	50 62+	12+	12+	0	12+	12+	0	0	100
MEAN TOTAL A. 75 B. 43	38	27 51	24	27	8	6	6	6 70	65	29

* Tension: 1. Controlled without miotics (under 25 mm. Hg Schiøtz). 2. With miotics. 3. Reduced (25–35 mm. Hg). 4. Hypotonic. 5. Uncontrolled.
† Visual fields: 1. Improved. 2. Unchanged. 3. Decreased or lost.

for from two to four years are shown in Table 9.

DISCUSSION OF TABLE 9

In this small series of 38 eyes observed for from two to four years, retrociliary cycloelectrolysis was employed as a primary procedure in 75 percent of the eyes. Additional surgery was required in 43 percent of the eyes to control the tension of 51 percent of the 38 eyes. These results are inferior to those obtained following anterior cycloelectrolysis where the eyes were observed over a longer period of time (12 years), where fewer were primary procedures (47 percent), and a smaller percentage of eyes required additional surgery (26 percent) to control the tension in 65 percent of 388 eyes. It has also been observed experimentally[17] that retrociliary cycloelectrolysis or cyclodiathermy are not as effective as anterior cycloelectrolysis or anterior cyclodiathermy. Our studies[12,13] have also indicated that anterior cycloelectrolysis (catholysis) has produced more prolonged control of tension in human eyes than does cyclodiathermy, with fewer complications, especially atrophy of the eyeball.

EXPERIMENTAL STUDY OF CYCLODIATHERMY AND CYCLOELECTROLYSIS

A controlled experimental study of 55 normal rabbit's eyes was reported by Sheppard[16] who concedes that the structures of the rabbit eye vary from those of the human eye, but certain observations made on the rabbit eye may be applied in treating the human.

Comparative observations using anterior cyclodiathermy (40 ma. for five seconds) on the right eye and anterior cycloelectrolysis (five ma. for five seconds) on the left eye

(applications in both procedures placed between two and four mm. from the cornea) gave the following findings:

1. The mean intraocular pressure was decreased with either method for *six months* postoperatively.

2. The most serious complication was phthisis bulbi which occurred in five of the 55 eyes treated with cyclodiathermy (9.9 percent) and in only one of the 55 eyes treated with cycloelectrolysis (1.8 percent).

In a separate series,[17] 53 normal rabbits' eyes were treated comparatively using retrociliary cyclodiathermy on the right eye and retrociliary cycloelectrolysis on the left eye. Observations were as follows:

1. The intraocular pressure was reduced for approximately *six weeks* postoperatively using either method, as compared with six months using the anterior procedures.

2. The postoperative histologic changes were similar with these two retrociliary methods.

When anterior cycloelectrolysis and anterior cyclodiathermy were compared with the retrociliary counterparts, the following were observed:

1. The anterior method showed more extensive involvement of the ciliary body and ciliary processes than the retrociliary method.

2. That the anterior applications substantially reduced the intraocular pressure for a longer period than the retrociliary method.

Postoperative complications of cyclodiathermy and cycloelectrolysis

Postoperative complications in retained eyes following anterior and retrociliary cyclodiathermy and anterior and retrociliary cycloelectrolysis are tabulated in Table 10.

Discussion of Table 10

In evaluating the postoperative complications of the various techniques, an important factor to be considered is the number of years the eyes have been observed following surgery. In anterior nonpenetrating cyclodiathermy, the majority of the eyes were observed postoperatively for from one to two years, and a few up to eight years. Atrophy occurred in three percent, and phthisis bulbi in three percent of the eyes. In the retained 304 eyes observed for from three months to four years following anterior penetrating cyclodiathermy, atrophy occurred in five percent and phthisis bulbi in an additional two percent of the eyes. Atrophy occurred in seven percent of the 659 eyes observed for from two months to 14 years following nonpenetrating retrociliary diathermy, and phthisis bulbi was reported in two percent of the eyes. However, in Weve's series of 154 cases of nonpenetrating retrociliary diathermy observed for from one to 14 years postoperatively, atrophy occurred in 23 percent of 144 retained eyes, and phthisis bulbi in two percent of this series of cases. Of particular interest are the cases of buphthalmos tabulated in Table 5, 57 of which were submitted by Weve. Atrophy occurred in 26 percent of these 53 retained eyes and phthisis bulbi in six percent.

In the series of 539 eyes observed for from one month to six years following penetrating retrociliary diathermy, the majority of cases were observed only for from one to two years postoperatively. Atrophy occurred in three percent and phthisis bulbi in three percent of the 539 eyes.

The percentage of these serious complications evidently increases with time as indicated by a previous report[13] in which 13 percent of 223 retained eyes observed for from one to 14 years, became atrophic following anterior cyclodiathermy. Atrophy occurred in 6.5 percent of 114 eyes observed for from one to five years following retrociliary diathermy. The high incidence of atrophy following cyclodiathermy has also been observed by deRoetth[18] (20 percent); Lachman and Rockwell[19] (over 15 percent); Calamandreie,* Goar,* Rychener,* Miller,* Offret* and others.

* Response to questionnaire, 1958.

TABLE 10

POSTOPERATIVE COMPLICATIONS IN RETAINED EYES FOLLOWING CYCLODIATHERMY AND CYCLOELECTROLYSIS

Complications	Technique employed and number of eyes* (percent)						
	A	B	C	D	E	F	G
Atrophic globes	4–3	15–5	46–7	16–3	0	2 eyes	0
Phthisis bulbi	4–3	7–2	15–2	15–3	0	1 eye	0
Absolute glaucoma	16–10	18–6	37–5	35–6	0	8–3	0
Iritis	0	14–4	18–3	14–3	19–6	1 eye	0
Cataract	3–2	1 eye	34–5	9–2	0	0	0
Dislocated lens	0	0	1 eye	0	0	0	0
Hemorrhage-anterior chamber	1 eye	20–7	34–5	29–5	33–10	0	0
Vitreous hemorrhage	1 eye	6–2	7–1	9–2	0	1 eye	0
Bullous keratitis	3–2	6–2	14–2	5–1	0	0	0
Retinal detachment	1 eye	0	7–1	1 eye	0	0	0
Corneal necrosis	1 eye	0	4 eyes	3 eyes	0	2 eyes	0
Iridocyclitis	0	3–1	7–1	3 eyes	0	3–1	0
Ruptured choroid	0	0	2 eyes	0	0	0	0
Synechias	0	0	5 eyes	0	0	0	0
Uveitis	1 eye	0	4 eyes	0	0	0	0
Interstitial keratitis	0	1 eye	1 eye	0	0	0	0
Bullous keratitis	1 eye	1 eye	1 eye	1 eye	0	0	0
Ribbon keratitis	0	1 eye	2 eyes	5–1	0	2 eyes	0
Corneal ulcer	0	1 eye	0	1 eye	0	0	0
Corneal erosion	0	0	0	0	0	3 eyes	0

*TECHNIQUE	EYES	OBSERVED FOR
A. Anterior nonpenetrating cyclodiathermy	161	1 to 8 yr.
B. Anterior penetrating cyclodiathermy	304	3 mo. to 4 yr.
C. Nonpenetrating retrociliary diathermy	659	2 mo. to 14 yr.
D. Penetrating retrociliary diathermy	539	1 mo. to 6 yr.
E. Anterior-posterior nonpenetrating diathermy & cyclodialysis (Čavka)	324	1 to 7 yr.
F. Anterior cycloelectrolysis	373	1 to 12 yr.
G. Retrociliary cyclodlectrolysis	36	2 to 4 yr.

Atrophy was observed in only two eyes (0.5 percent) of 373 eyes observed for from one to 12 years following anterior cycloelectrolysis, and phthisis bulbi in only one eye. Although no serious complications were reported following retrociliary cycloelectrolysis in the small series of 36 retained eyes, these cases have been observed for too short a period of time (two to four years) to compare these results with those of the other techniques observed for a much longer period of time.

The incidence of absolute glaucoma was 10 percent in nonpenetrating cyclodiathermy, six percent following anterior penetrating diathermy, six percent in penetrating cyclodiathermy, five percent in nonpenetrating retrociliary diathermy and three percent in anterior cycloelectrolysis.

Cataract occurred more frequently following nonpenetrating retrociliary diathermy than following nonpenetrating anterior or penetrating retrociliary diathermy (five percent) where this complication occurred in two percent of the eyes following either technique.

Bullous keratitis was reported in two percent of the eyes following anterior nonpenetrating cyclodiathermy, anterior penetrating cyclodiathermy and nonpenetrating retrociliary diathermy and in one percent following penetrating retrociliary diathermy.

Hemorrhage into the anterior chamber was greatest following Čavka's technique (10 percent) and occurred in five percent of the eyes following nonpenetrating and penetrating retrociliary diathermy and in seven percent of the eyes following anterior penetrating cyclodiathermy.

From the data tabulated in Table 10, it would appear that more serious complications occur following retrociliary penetrating and nonpenetrating cyclodiathermy. Comparatively few complications occur follow-

ing Čavka's combined operation, none following retrociliary cycloelectrolysis, and a minimum of serious complications following anterior cycloelectrolysis.

Summary

The data submitted by members of the French Ophthalmological Society and of the American Ophthalmological Society, revealed a trend toward nonpenetrating retrociliary diathermy (700 eyes) and penetrating retrociliary diathermy (570 eyes) as compared with nonpenetrating anterior cyclodiathermy (174 eyes) and penetrating anterior cyclodiathermy (320 eyes).

The majority of the eyes tabulated in Tables 3 to 7 (the various diathermy procedures) were observed for from one to two years, many under one year, and a minimum up to 14 years. This fact must be considered in evaluating the postoperative results and complications following the various procedures since cyclodiathermy (as well as cycloelectrolysis) loses its effectiveness over the years with more reoperations required as time goes on, as well as more serious long range postoperative complications, particularly atrophy and phthisis bulbi.

Tension was controlled under 25 mm. Hg (Schiøtz) (with and without miotics) in the following procedures which were employed as primary operations in over 75 percent of the eyes:

	Eyes	Percent
1. Nonpenetrating anterior cyclodiathermy	174	29
2. Penetrating anterior cyclodiathermy	320	39
3. Nonpenetrating retrociliary diathermy	700	45
4. Penetrating retrociliary diathermy	570	44

Anterior and posterior nonpenetrating cyclodiathermy combined with cyclodialysis was used by Čavka as a *primary procedure* in 324 eyes and tension was controlled in 73 percent of the eyes, with and without miotics.

Anterior cycloelectrolysis was employed as a primary procedure in only 47 percent of 388 eyes observed for from one to 12 years (the majority observed for from three to six years). Tension was controlled under 25 mm. Hg (Schiøtz) in 65 percent of the eyes, with and without miotics.

Retrociliary cycloelectrolysis was used as a primary procedure in 75 percent of 38 eyes observed for from two to four years postoperatively with tension controlled in 51 percent of the eyes.

Visual fields were improved or unchanged in 36 percent of the eyes following nonpenetrating anterior cyclodiathermy; in 56 percent following penetrating anterior cyclodiathermy; in 34 percent following nonpenetrating retrociliary diathermy; in 46 percent following penetrating retrociliary diathermy; in 95 percent following Čavka's procedure of anterior and posterior nonpenetrating cyclodiathermy combined with cyclodialysis; in 58 percent following anterior cycloelectrolysis and in 71 percent following retrociliary cycloelectrolysis.

Atrophy of the globe continues to be a serious complication following penetrating and nonpenetrating cyclodiathermy and retrociliary diathermy, with individual reports ranging from two percent to 26 percent of the eyes in which this complication occurred.

The incidence of atrophy occurred more frequently following nonpenetrating retrociliary diathermy as shown by the following comparisons:

	Atrophy (percent)	Phthisis Bulbi (percent)
1. Anterior nonpenetrating cyclodiathermy	3	3
2. Anterior penetrating cyclodiathermy	5	2
3. Nonpenetrating retrociliary diathermy	7	2
4. Nonpenetrating retrociliary diathermy	3	3
5. Anterior cycloelectrolysis	0.05	1 eye

The more serious complications were observed following retrociliary penetrating and nonpenetrating diathermy, as tabulated in Table 10, and comparatively few complications occurred following Čavka's technique and following cycloelectrolysis.

Conclusions

The effectiveness of both cyclodiathermy and cycloelectrolysis decreases with the length of postoperative observation but to a lesser degree following the latter procedure. The high percentage of atrophy (from two to 26 percent) in 1,662 retained eyes following cyclodiathermy as compared with only two eyes of the 409 retained eyes following cycloelectrolysis, suggests that diathermy should be used with caution.

Cyclodiathermy and cycloelectrolysis should be reserved for those eyes in which filtering or other operations are contraindicated or have failed.

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Ophthalmic Miniature

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NEWER ANTIBIOTICS: THEIR INTRAOCULAR PENETRATION*

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In spite of the many reports in the literature concerning the ocular penetration of antibiotics in both experimental animals and humans, it is difficult to compare their penetration from reported results. The amounts of antibiotic detected by these studies appear in terms of units, micrograms or simply as pluses ranging from 1+ to 4+.[1] This is not surprising, however, as the techniques and methods of drug assay vary not only for different antibiotics but even for the same one. Determinations are usually made by employing chemical, colorimetric, and microbiologic techniques.

When considering bioassay methods, the technique may involve tube serial dilution, cup-plate, semimicroagar diffusion and other methods. Furthermore, test microorganisms differ in their sensitivity from one species to another and from strain to strain.

These factors are responsible for the variation in reported results as exemplified in the case of chloramphenicol. Abraham, et al.,[2] and Langham,[3] in evaluating the ocular penetration of this drug, utilized a chemical colorimetric method[4] of drug assay dependent on the reduction of the aromatic nitro-radical to a primary amine and subsequent diazotization with the Bratton-Marshall reagent. The amounts found in tissue fluid depend on color differences compared with a standard. This method may not readily distinguish the active antibiotic molecule from inactive degradation products containing the aromatic nitro-radical.

Although a solvent extraction procedure is more specific, its values are only in fair agreement with a microbiologic method. Sorsby, et al.,[5] determining penetration of the same drug, found lower values than the previous authors. They utilized a microbiologic method of assay with Shigella sonnei as the test organism.

Leopold and coworkers,[6] who initially evaluated the ocular penetration of chloramphenicol, used a cup method of bioassay as described by Randall, et al.[7] Finally, Bleeker and Maas[8] employed the tube serial dilution method of Goslings,[9] while Crabb, Fielding and Ormsby[10] used still another method.

It is not surprising, therefore, that critical review of these reports shows some variance in the ease and degree of ocular penetration when these studies are compared.

The search for new antibiotics is continuing and recently several have become available for ocular evaluation. One new antibiotic, spiramycin,[11] has been evaluated for its ocular penetrability. In attempting to compare this antibiotic with others previously reported, the problems produced by the utilization of divergent methods of assay became apparent.

The purpose of this paper is to report the following results:

1. Ocular penetration of spiramycin, ristocetin, kanamycin and chloramphenicol, using a single microbiologic method of drug assay and utilizing the same tube serial dilution method and the same test organism.

2. Penetration of these agents through the chemically inflamed eye which presents a more permeable blood-ocular barrier.

3. The ether/water partition coefficient of these antibiotics.

D-glucosamine, a simple amino sugar reported to enhance the blood level of anti-

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biotics administered by other routes,[12] was included in this study to determine whether it effected ocular penetration of these antibiotics when simultaneously administered.

Materials and Methods

A bioassay procedure was used in which the growth-inhibiting property of the four antibiotics was tested against Bacillus subtilis (ATCC 6633). Although several strains of staphylococci were considered in this study, they did not possess the combined level of sensitivity to the four drugs as did B. subtilis (#6633).

The procedure followed was the serial broth dilution method used in previous work[13, 14] but it most closely parallels that used recently in the study on spiramycin[13] in which a large improvement of the sensitivity of the method was achieved. An additional twofold improvement is made in the current work, complete details of which are given below.

The major problem in bioassays on ocular fluids, particularly that of the aqueous humor, is the small volume of the fluid (0.2 ml. or less) that is available. In order to obtain optimal sensitivity of the method there are two factors that can be manipulated to best advantage: (a) the use of a maximum volume of the test fluid and (b) a minimal volume of broth culture medium, and inoculum. In so doing it is possible to minimize the amount of dilution in the all important initial tube while maintaining sufficient volume of nutrient broth for observation of growth inhibition results. The best results were obtained by pooling the test fluids from four eyes of two identically treated rabbits and using 0.5 ml. of broth culture fluid in Wassermann (13 by 100 mm.) tubes. Aqueous and vitreous were drawn from the living animal as described elsewhere.[13]

Trypticase-soy broth (Difco) was pipetted into individual tubes 0.5 ml./tube. The first tube differed in that double strength broth was used to make up for the initial dilution of the nutrient. Test fluid (0.5 ml.) was added to the first tube, mixed, and 0.5 ml. carried serially in successive tubes (using a new pipette for each tube) to give twofold dilutions of the fluid to be tested. By this procedure it was possible to test the aqueous and vitreous at no lower a dilution than 1:2. Dilutions were usually carried out for five tubes for aqueous, three tubes for vitreous and 10 tubes for serum.

Standard controls on the antibiotics were always carried out by an arithmetic progression. If the sensitivity of a drug, for example, spiramycin was in the range of 3.0 μg./ml., than the progression was arranged with increments of 1.0 μg./ml. The inoculum consisted of 30,000 viable cells per tube and was prepared from a 16-20 rour growth of B. subtilis cultured on Difco stock culture agar. A bacterial suspension in 0.85-percent saline with an optical density of 70 on the Klett-Summerson photoelectric colorimeter (No. 54 green filter), was freshly prepared prior to each experiment, diluted to 1:5 in saline, and used at 0.025 ml. per tube.

Results were determined by comparing the growth or lack of growth in the culture tubes at the end of 20 hours. An initial reading after only 16 hours was used only in those instances where it would supplement equivocal results at the later period.

The sensitivity of the method was dependent not only on minimizing the dilution established in the first tube as already mentioned—being held constant for all antibiotics under examination—but was also dependent on the biologic, chemical, and physical characteristics of the individual antibiotics. It may be noted in the tables that the values of the standard varies in the cases of kanamycin and ristocetin. The variation was due in part to the instability of these agents. Color changes were apparent from one vial to another depending on age of the sample and temperature of storage. According to the method used above the detectable amount of a given drug in aqueous humor, or other fluid, would be two times the value (that is,

reciprocal of the initial tube dilution) of the "standard" or control value given in the tables.

The ether/water partition coefficient of the antibiotics was determined by making up a 2.5-percent solution of each in phosphate buffer, 0.01, M, pH 7.2. Two ml. of the 2.5-percent solution was added to 3.0 ml. of ether in a sterile separatory funnel. This was done for each antibiotic. The four funnels were placed in a reciprocating-shaker and agitated for two hours. One ml. of the ether layers was removed and placed in a sterile flask and allowed to evaporate overnight at refrigerated temperature. One ml. of the buffer partition was removed from which twofold serial dilutions were made in Trypticase-soy broth as previously described. The buffer partition was evaluated the same day using the same fresh culture of B. subtilis. The ether partition was evaluated the following day by adding buffer to the residue in the flask after the ether had completely evaporated. From this one ml. of material was removed and subjected to the bioassay technique.

Results

In a comparative study of drugs it is ideal when identical dosage and route of administration can be studied for a given time interval. However, this becomes impractical for some drugs, especially when they are recommended only for a given route of administration or contraindicated for other routes because of discomfort or because of local or systemic toxicity. Kanamycin, for example, is recommended systemically by intramuscular route, absorption being poor when the drug is given orally. Ristocetin is limited to intravenous use and contraindicated for oral or intramuscular administration. Spiramycin has been given orally, the intramuscular or intravenous routes having as yet not been established or defined.

Considering these limitations, this study was carried out in an effort to determine drug penetration in the animal eye when the antibiotic is administered in a dose and route equivalent to that recommended in the human. In those instances in which no penetration of the ocular fluids was found, the dosage was increased or the route altered from that recommended in an effort to determine whether the antibiotic is capable of ocular penetration under these conditions.

Routes of administration in rabbits

Intramuscular administration (table 1). When kanamycin is administered in a dose of 15 mg./kg. of body weight intramuscularly (equivalent to average human dose of 1.05 gm.), there is no detectable penetration of the drug into the aqueous or vitreous after one, two, or four hours, although a serum level of 16 μg./ml. is found at the end of two hours and 6.0 μg./ml. after four hours.

By increasing the initial does of kanamycin to 50 mg./kg. of body weight and repeating the same dose after one hour, a minimal amount (1.6 μg./ml.), can be detected

TABLE 1

Intramuscular administration of kanamycin

Dose	Time*	Aqueous (μg./cc.)	Vitreous (μg./cc.)	Serum (μg./cc.)	Standard
15 mg./kg.	1 hr.	0	0	—	1.0
	2 hr.	0	0	16	
	4 hr.	0	0	6	0.8
50 mg./kg.†	75 min.	1.6	0	26	0.8

* Time indicates the time interval between initial administration of the drug and the removal of the aqueous, viterous or serum.

† Indicates the same dose was administered a second time one hour later.

TABLE 2

INTRAVENOUS ADMINISTRATION OF ANTIBIOTICS

Drug	Dose	Time*	Aqueous (μg./ml.)	Vitreous (μg./ml.)	Serum (μg./ml.)	Standard (μg./ml.)
Kanamycin	50 mg./kg.	15 min.	4 or less	0	128	0.5
		1 hr.	8 to 16	0	128–256	4
Chloramphenicol	15 mg./kg.	30 min.	0	0	—	—
		1 hr.	0	0	20	2
	50 mg./kg.	45 min.	6	0	8 to 12	2
	50 mg./kg.	75 min.	12	6 or less	48	3
Spiramycin	50 mg./kg.	1 hr.	0	0	24	3
	50 mg./kg.	75 min.	6	6	96	3
Ristocetin	50 mg./kg.	15 min.	0	0	307	0.6
		30 min.	—	—	256	0.4
	50 mg./kg.†	75 min.	0	0	410	0.8

* Time indicates the time interval between initial administration of the drug and the removal of the aqueous, vitreous or serum.

† Indicates the same dose was administered a second time one hour later.

in the aqueous 75 minutes after the initial dose. None is found in the vitreous, but 26 μg./ml. are found in the serum.

Intravenous administration (tables 2 and 3). Intravenous administration of 50 mg./kg. of kanamycin (equivalent to average human dose of 3.5 gm.) produces 4.0 μg./ml. or less in the aqueous after 15 minutes, none in the vitreous, and a serum level of 128 to 256 μg./ml. After one hour, 8.0 to 16 μg./ml. are found in the aqueous, none in the vitreous, and up to 256 μg./ml. in the serum.

When 50 mg./kg. of kanamycin was injected intravenously immediately preceded by 25 mg./kg. of d-glucosamine, 0.0 to 2.0 μg./ml. of the antibiotic was found in the aqueous, none in the vitreous, and 25 to 100 μg./ml. in the serum after 15 minutes. There were no detectable ocular fluid levels of spiramycin or ristocetin when similarly given.

Chloramphenicol administered in a dose of 15 mg./kg. (equivalent to a human dose of 1.05 gm.) gave no detectable levels of antibiotic in the aqueous or vitreous after 30 minutes and one hour. The serum level after one hour is found to be 20 μg./ml. When the dosage is increased to 50 mg./kg. (equivalent to a human dose of 3.5 gm.), only 6.0 μg./ml. of chloramphenicol were detectable in the aqueous, none in the vitreous, and 8.0 to 12 μg./ml. in the serum after

TABLE 3

INTRAVENOUS ADMINISTRATION OF ANTIBIOTICS PRECEDED BY 25 MG./KG. OF D-GLUCOSAMINE

	Dose	Time*	Aqueous (μg./cc.)	Vitreous (μg./cc.)	Serum (μg./cc.)	Standard
Kanamycin	50 mg./kg.	15 min.	0	0	25	0.8
			2	0	100	0.25
Spiramycin	50 mg./kg.	15 min.	0	0	24 or less	3
		1 hr.	—	—	12 or less	3
Ristocetin	50 mg./kg.	15–20 min.	0	0	200	2
		15 min.	0	0	307	0.6
		1 hr.	—	—	153	0.6

* Time indicates the time interval between initial administration of the drug and the removal of the aqueous, vitreous or serum.

TABLE 4

SUBCONJUNCTIVAL ADMINISTRATION OF ANTIBIOTICS

	Dose	Time*	Aqueous (μg./cc.)	Vitreous (μg./cc.)	Serum (μg./cc.)	Standard
Kanamycin	10 mg.	1 hr.	8	0	—	1
			8	4	—	1
	20 mg.	1 hr.	10	0	—	5
Spiramycin	20 mg.	1 hr.	24	6	—	3
Ristocetin	10 mg.	1 hr.	0	0	—	0.5
	5 mg.	1 hr.	0	0	—	0.5

* Time indicates the time interval between initial administration of the drug and the removal of the aqueous, vitreous or serum.

45 minutes. This same dose repeated after one hour gives 12 μg./ml. detectable in the aqueous, 6.0 μg./ml. or less in the vitreous, and a serum level of approximately 48 μg./ml. (75 minutes after initial dose).

Intravenous administration of 50 mg./kg. of spiramycin produced no antibiotic levels in the aqueous or vitreous and 24 μg./ml. in the serum after one hour. This same dose repeated after one hour yields 6.0 μg./ml. in the aqueous, 6.0 μg./ml. in the vitreous, and up to 96 μg./ml. in the serum after 75 minutes.

Ristocetin administered intravenously in a dose of 50 mg./kg. of body weight (equivalent to human dose of 3.5 gm.) results in approximately 256 μg./ml. in the serum after 30 minutes. No detectable drug levels were found in the aqueous or vitreous after 15 minutes. Repeating this dose again after one hour increases the serum level to more than 410 μg./ml. 75 minutes after the initial dose although no levels are found in the aqueous or vitreous at this time.

Subconjunctival administration (table 4). Kanamycin injected subconjunctivally in a total dose of 10 mg. produces 8.0 μg./ml. in the aqueous and none in the vitreous after one hour. Increasing the dose to 20 mg. yields 8.0 to 10 μg./ml. in the aqueous and 4.0 μg./ml. or less in the vitreous after one hour.

A subconjunctival dose of 20 mg. of spiramycin produces 24 μg./ml. in the aqueous and 6.0 μg./ml. in the vitreous after one hour.

Ristocetin in a 5.0 or 10 mg. dose did not penetrate the ocular fluids.

Oral administration (table 5). Chloramphenicol was given orally in a dose of 45 mg./kg. body weight (equivalent to a human does of 3.15 gm.). Neither aqueous or vitreous levels were detectable after one hour when approximately 20 μg./ml. were detected in the serum.

When the oral dose was approximately

TABLE 5

ORAL ADMINISTRATION IN RABBITS

Drug	Dose	Time*	Aqueous	Vitreous	Serum	Standard
Chloramphenicol	45 mg./kg.	1 hr.	0	0	20	2
	85 mg./kg.	1 hr., 20 min.	0	0	0	2
		2 hr.	0	0	8	2
		4 hr.	4	0	16	
		6 hr.	0	0	16	
	85 mg./kg.	1¾ hr.	0–6 34 μg./gm. in uveal tissue	0	16	3

* Time indicates the time interval between initial administration of the drug and the removal of the aqueous, vitreous or serum.

doubled (equivalent to a human dose of 6.0 gm.), it will be noted in Table 5 that only 4.0 μg./ml. were detectable in the aqueous after 4 hours, and none detectable at two or six hours in either aqueous or vitreous. The serum concentration at six hours was 16 μg./ml.

One and three quarter hours after on oral dose of 85 mg./kg. of spiramycin was administered 0.0 to 6.0 μg./ml. of antibiotic could be found in the aqueous and none could be detected in the vitreous fluid. The serum contained 16 μg./ml.

Spiramycin in uveal tissues

The content of spiramycin in the uveal tissue was determined in one experiment involving pooled uveal tissues from four rabbit eyes. Two rabbits were given 85 mg. of the drug orally and after two hours the animals were killed and suspended vertically to allow the blood to drain from the head for two hours. The uvea were removed aseptically and after rinsing three times in saline they were drained, weighed in wet condition, homogenized, taken up in 1.0 ml. saline and centrifuged. One-half ml. of the supernate was mixed with an equal volume of broth and the assay procedure followed. The result was growth inhibition in the first 1 : 2 tube dilution and calculations indicated a value for spiramycin of 34 μg./gm. wet weight of uveal tissue. If the tissue specific gravity is close to that of serum then a comparison with the serum level of the drug of 16 μg./ml. suggests an approximate twofold concentration of spiramycin in the uvea. No further experiments were made and therefore no conclusive evidence is offered for this interesting possibility.

Spiramycin has been reported by Garin and Eyles[15] and Bogacz[16] to be effective in animals in protecting them from fatal doses of toxoplasma. Based on these reports the fact that spiramycin was found to penetrate the ocular fluid when administered in large doses, and suggestive evidence in our laboratory that this agent permeates the uveal tissue, it is being clinically employed in suspected cases of toxoplasmic uveitis.

TABLE 6

Oral administration in humans

	Dose	Time	Aqueous	Serum
Spiramycin	3 gm.	1½ hr.	0	12
	3 gm.	1½ hr.	0	6
	6 gm.	13½ hr.	6	— (not taken)

TABLE 7

Penetration into inflamed rabbit eyes

	Dose	Aqueous	Vitreous	Time
Kanamycin	15 mg./kg. (i.m.)	3.2–16	0	2 hr.
Spiramycin	50 mg./kg. (p.o.)	12	0	2 hr.
Ristocetin	50 mg./kg. (i.v.)	0	0	2 hr.

Oral administration of spiramycin in humans (table 6). Two patients were each given a single dose of 3.0 gm. of spiramycin orally prior to cataract surgery. Aqueous humor was removed one and one-half and one and three-quarter hours following medication. No detectable drug was found in the aqueous although the serum levels ranged from 6.0 μg./ml. to 12 μg./ml.

One patient with posterior uveitis was given 3.0 gm. by mouth initially followed by 1.0 gm. every four hours for 12 hours. Approximately 13 hours after the first dose a sample of aqueous humor contained 6.0 μg./ml. of spiramycin. This result may have been due to a more permeable blood-ocular barrier caused by uveal inflammation.

Ocular penetration in the inflamed rabbit eye (table 7). The anterior segment of rabbit eyes was inflamed by "burning" the corneas with concentrated hydrochloric acid. The purpose was to increase the permeability of the blood-ocular barrier and determine the penetration of kanamycin, spiramycin and ristocetin under these conditions. The route used was that recommended for the particular agent. Table 7 shows that both kanamycin and spiramycin penetrate the aqueous humor after two hours. Kanamycin

when given 15 mg./kg. intramuscularly attains a level of 3.2 to 16 μg./ml. in the aqueous. Spiramycin given 50 mg./kg. by mouth penetrates the aqueous to the extent of 12 μg./ml. Ristocetin given 50 mg./kg. intravenously gave no detectable aqueous levels after two hours.

Discussion

Studies of the characteristics of the blood-ocular barriers have been made by many authors.[17-19] Their work suggests that increased fat solubility, molecular weight of less than 500, and low degree of ionization are features which favor penetration of antibiotics and other substances through the blood-ocular barriers. Langham has reported that the ether/water partition coefficient of some antibiotics and chemotherapeutic agents was related to the rate of entry of these substances into the ocular fluids. That is, substances such as chloramphenicol which penetrated the blood-ocular barriers had a higher ether/water partition coefficient than sulfonamides or penicillin whose coefficients were respectively lower. In recent work by Bleeker and Maas[20] two types of penicillin were compared for ocular penetrability. One of these, penethamate (the diethylamino ethyl ester of penicillin) was found to be superior to procaine penicillin, and they related this result to a higher ether/water partition coefficient of the former antibiotic.

This study was not intended to determine the correlation of ether/water partition coefficients of the substances used with their rate of entry. In order to do so samples of aqueous at a steady-state condition would have been necessary and would have to be achieved by maintaining rather constant uniform plasma levels of each antibiotic. This was not attempted here. However, if one were to correlate the ether/water coefficients found for these antibiotics with the data obtained on aqueous penetration by the intravenous route, a definite trend would be apparent.

TABLE 8

Correlation of ether/water partition coefficients

Antibiotic 50 mg./kg. (i.v.)	Approximate Aqueous and Serum Levels after One Hour (μg./ml.)		Ether/Water Partition Coefficient
	Aqueous	Serum	
Kanamycin	4 or less	128	<0.001
Ristocetin	<0.6	153	0.005
Chloramphenicol	<2.0	20	3.2
Spiramycin	<3.0	24	5.0

For example, for kanamycin and ristocetin the data (table 8) show that at the end of one hour there is a very small degree of aqueous penetration when compared to the very high levels found in the serum. This low degree of penetration correlates with a low ether/water partition coefficient. On the other hand, taking chloramphenicol and spiramycin, it is apparent that the aqueous penetration is rather high when compared to a much lower serum level of these substances. This higher degree of penetration based on aqueous/serum ratio correlates with a higher ether/water coefficient for these two substances.

The figures, therefore, do suggest that the degree of penetration of these substances into the aqueous is related to the ether/water partition coefficients, and, therefore, is in agreement with the work of Langham, Bleeker and Maas. One might argue that the correlation fails if the magnitude of the partition coefficients and aqueous penetration levels alone are considered because in that case the degree of penetration for the individual substances with their ether/water coefficients shows less apparent relationship. The true relationship will have to be resolved by additional investigations based on steady-state aqueous and plasma ratios.

Summary and Conclusions

1. This study indicates that exceedingly large systemic doses of the new antibiotics are necessary to achieve ocular penetration. Based on the time periods studied (one,

two, four and six hours) and the small amounts detectable in the ocular fluids, it may be concluded that these agents have difficulty permeating the normal blood-ocular barriers.

2. Only spiramycin and chloramphenicol were administered orally; kanamycin and ristocetin given by this route are poorly absorbed. In animals, spiramycin was found in the aqueous after 1.75 hours following an equivalent human dose of 6.0 gm. The same dose of chloramphenicol in animals penetrated the aqueous after four hours. Samples taken at one, two and six hours showed no detectable antibiotic. By the method of assay used in this investigation, it may be concluded that chloramphenicol does not pass the blood-ocular barrier as readily as previously reported.

2. When administered intravenously there is no real difference between kanamycin, chloramphenicol and spiramycin despite the fact that the data indicate better aqueous penetration by kanamycin and least by spiramycin. The aqueous values noted represent a single tube dilution difference. This factor which is within the limits of error of the method, plus the variation in the standard, account for the slight differences in aqueous values. Intravenously ristocetin gave the highest blood levels but no ocular penetration.

4. Subconjunctival administration in animals gave good penetration. Spiramycin was superior to kanamycin, both drugs being able to permeate the vitreous as well when a 20-mg. dose is used. Ristocetin gave no penetration when injected beneath the conjunctiva.

5. Intramuscular kanamycin in rabbits penetrates the normal eye poorly even when given in large doses.

6. Both kanamycin and spiramycin are capable of penetrating the aqueous humor of the inflamed animal eye. Kanamycin was given approximately 15 mg./kg. intramuscularly and spiramycin 50 mg./kg. orally.

7. In two cataract patients receiving orally 3.0 gm. each of spiramycin, none was detected in the aqueous after 1.5 hours. One patient with posterior uveitis who received 6.0 gm. of spiramycin orally had 6.0 μg./ml. of drug in the aqueous some 13 hours after the start of therapy. This may be due to the increased permeability of the blood-aqueous barrier in uveitis.

8. The ether/water partition coefficients of these substances seem to be related to their degree of penetration.

9. D-glucosamine had no influence on ocular penetration of these antibiotics, according to the method used and for the time period studied.

10. It is suggested that a single uniform method be used when possible for comparing different antibiotics for their penetration into the eye.

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SYSTEMIC EFFECTS OF CO-RAL AND CORALOX*

On ocular instillation in the rabbit, dog, and human

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Ocular administration of anticholinesterase compounds has been reported to produce no systemic effects by several investigators (Grant, 1948[1] Thiel, 1949[2] Knupffer, 1949[3] and Heurkamp and Wagner, 1950[4]). Krishna and Leopold[5] recently reported reduction in "true" red blood cell cholinesterase levels in humans with Phospholine Iodide, used in the treatment of glaucoma. In a study of the toxicology and pharmacology of an anticholinesterase insecticide, Co-Ral and its oxygen analogue, coralox, it was believed desirable to study the systemic effects of ocular administration of the oxygen analogue, which is a potent miotic agent, and also that of the sulfur analogue, Co-Ral, which has little if any miotic action. Co-Ral is used for the control of ectoparasites. Chemically it is diethyl-0-3-chlor-4-methyl-7-coumarinyl phosphorthionate. The oxygen analogue, coralox, is the active metabolite of Co-Ral, and is produced in the liver by replacement of the sulfur by an oxygen atom. Coralox has no commercial use. The toxicology and pharmacology of these two compounds have been investigated by Du-Bois, et. al.[6] by the oral and injected routes of administration. This study was made to observe the systemic effects of these compounds when instilled into the conjunctival sac of rabbits, humans and dogs, in 0.25-percent solution in peanut oil.

The absorption of polyalkylophosphates in the eye depends on the solubility, the solvent and the dosage. Neither of these compounds is water soluble, but both are soluble in oils. The solutions were prepared in 0.25-percent concentration in peanut oil. It is assumed that these compounds or any eyedrops pass through the lacrimal system and disperse on the nasal mucosa, where absorption occurs to the largest extent. A study of the

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distribution of oil drops instilled into the eyes of rabbits revealed that not only did these drops pass through the lacrimal system but they were readily found in the bronchi and lung tissue of the rabbit. Solutions labelled by dyes and by fluorescein could be readily detected, showing that systemic absorption through this route occurs readily in the rabbit. It is well known that nasal sprays in the rabbit are found to be widely distributed in the lung. Oil nose drops are not advised in humans because of oil inclusions in the lungs following use of this type of preparation. Advice commonly given for instillation of eyedrops includes directions to apply pressure to the punctum lacrimalis to prevent passage of the medication into the nose. This could not efficiently be done in rabbits or dogs.

Cholinesterase is an enzyme which is generally present in living tissue and, like all enzymes, is a simple or compound protein. Several types probably exist but one dominates. It is large-molecular, does not dialyze, but there is difference of opinion as to whether it is associated with the albumen or globulin fraction of blood. It is highly stable, and will retain activity for at least a week at room temperature (Walquist, 1935[7] Tourtellotte, 1948[8]). It acts as a catalyst in the hydrolysis of acetylcholine into choline and acetic acid.

The ability of the brain tissues to hydrolyze acetylcholine was noted by Plattner and Hintner[9] in 1930. Loewi and Navratil[10] had described the ability of other tissues to do this in 1926. In 1932, Stedman, Stedman and Easson[11] designated this esterase as acetylcholinesterase, believing it to be specific for acetylcholine. In 1935, the Stedmans[12] first observed that different areas of the brain had different rates of activity in hydrolyzing acetylcholine. In 1939, Nachmansohn[13] found that not only did the speed of hydrolysis vary, but the concentration of cholinesterase in the brain varied with the area of the brain and species studied.

Mendel and Rudney[14] demonstrated that the original cholinesterase of the Stedmans is in reality two esterases, designed "pseudocholinesterase" and "true cholinesterase." Pseudocholinesterase hydrolyzes not only esters of choline, but a variety of noncholine esters as well. It exhibits greatest activity in the presence of high concentrations of acetylcholine (above 300 mg. percent) and decreasing activity with diminishing concentrations. It hydrolyzes benzoylcholine chloride, but not methacholine. It is not present in brain or red blood cells, but in other tissues is mixed with true cholinesterase.

Mendel and Rudney[15] also showed that "true cholinesterase" acts exclusively on certain choline esters and exhibits maximum activity at low concentrations of acetylcholine (3.0 mg. percent approximately), while increasing concentrations result in progressively greater inhibition of the enzyme activity. It hydrolyzes methacholine, but not benzoylcholine.

Hawkins and Mendel[16] in 1947 found that in rabbit plasma there was a 56-percent content of pseudocholinesterase, while in human plasma the pseudocholinesterase made up 99 percent of the activity. Mazur and Bodansky[17] in 1946 showed that with DFP, the serum cholinesterase level in humans could be lowered to zero values with no symptoms of acetylcholine accumulation. Gunter and Mendel[18] in 1945 reported that true cholinesterase levels in the blood were correlated with symptoms at levels of 70 to 80 percent inhibition. Hawkins and Gunter[19] in 1946 indicated that in vivo, nonspecific (pseudo) cholinesterase plays no essential part in the hydrolysis of acetylcholine.

Cholinesterase is not a single enzyme but denotes a whole group of enzymes, not all necessarily specific for acetylcholine. Classification into specific and nonspecific, or true and pseudo is only relative, and chances are that in any given tissue there are several cholinesterases, but usually those of one or the other type predominate.

DeRoetth (1950)[20] found that muscle-containing and nerve-containing tissues of

the eye, that is, iris, ciliary body, retina, and muscle contain specific cholinesterase. He correlated chemical values with histologic examination. Nonspecific cholinesterase was observed in blood serum and secondary aqueous humor.

Tourtellotte[8] found that cholinesterase levels could be lowered to very low levels (one percent) when physostigmine was used to "protect" rodents against subsequent doses of DFP, whether the rat survived or not.

Koelle and Gilman (1949)[21] found that, in the dog, brain cholinesterase was more resistant to DFP than was red blood cell cholinesterase; while in the rat, the reverse was found.

Kewitz and Nachmansohn[22] reported that 2-PAM injected at the same time or shortly after DFP was capable of causing the cholinesterase levels in brain to fall to values as low as one percent.

Cholinesterase in brain tissue is "true" or "specific" cholinesterase. Tourtellotte[8] found that all the cholinesterase in the rat brain is true, except for three areas.

Similar values were obtained on a series of normal female blood samples. Values for red blood cell cholinesterase were 101.13 cmm./5.0 min. for females and 93.16 for males.

Method

Tissues were obtained from the same animals that were used for the ocular tissue study previously reported. The animals were killed by air embolism, and samples of brain, salivary gland and ileum were obtained, washed for at least an hour in distilled water, weighed after blotting, minced and then carefully homogenized in glass homogenizers. Blood was obtained in heparinized syringes prior to death, separated by centrifuging and then, after removing the serum, the red blood cells were washed in 50-percent buffer, centrifuged and used in 50-percent solution. This applied to blood obtained from rabbits, dogs and humans.

Normal values were established for rabbits using six animals. In the dog, pretreatment levels were observed, and used for comparison with levels of activity observed under treatment, as only three animals were studied. Human blood values were established for females by Tourtellotte and Odell[23] (25.8 cmm. CO_2 per 0.1 ml. serum per 5.0 min.). Ten human males who were examined routinely for exposure to polyalkylphosphates in industry, and with other normal blood obtained from the hospital laboratory, were used to establish normal values for males and females (table 4) (32.2 cmm. CO_2 per 0.1 ml. serum for males and 25.69 cmm. for females). Similar values were obtained on a series of normal female blood samples. Values for red blood cell cholinesterase were 101.13 cmm. CO_2 per 5.0 min. for females and 93.16 cmm. for males.

Solutions of Co-Ral and coralox were made up in 0.25-percent concentration in peanut oil and used in all species. Usually two drops were instilled into the right eye of each animal, and the left eye was used as a control.

Blood was drawn from dogs at weekly intervals. Blood was obtained from patients in clinic when they returned for routine checkup.

All blood samples were examined manometrically by the method of DuBois and Mangun.[24] Tissues were examined either by manometry or by the chemical method of Hestrin,[25] which uses hydroxylamine and ferric sulfate for colorimetric assay for acetylcholine, in the spectrophotometer.

Results

Cholinesterase inhibition by the action of coralox and Co-Ral was found to levels as low as 25 percent in brain tissue. Tables 1 and 2 give the results of assays for cholinesterase activity in rabbit brain, salivary gland and ileum, and serum and red blood cell fractions of the blood.

The marked level of inhibition in rabbit tissue and blood may be based on the absorption of these chemicals in the lung,

TABLE 1

CHOLINESTERASE ACTIVITY IN RABBIT BLOOD WHILE ON CORALOX TREATMENT, ON CO-RAL TREATMENT, AND AFTER STOPPING TREATMENT

Days of Treatment	No. animals	Cholinesterase Activity*					
		Serum Values	Mean Deviation	Percent of Normal	50% Red Blood Cell Values	Mean Deviation	Percent of Normal
Coralox Normal	6	11.36	±1.6	100	26.80	± 8.3	100
7	4	11.2	±6.4	98	24.26	± 8.0	84
14	4	8.83	±3.2	79	17.8	±10.1	66
28	4	5.4	±7.8	51	14.5	± 2.7	53
Co-Ral							
7	3	8.08	±3.9	70	21.54	± 7.2	80
After Stopping Treatment Coralox†							
10	3	7.09	±3.8	70	17.7	± 9.4	66
18	3	11.15	±6.1	98	23.5	± 8.0	88

* Expressed as cmm. CO_2 per 0.1 ml. per 5 min.
† 28 da. treatment with Coralox.

through drainage via the lacrimal system after instillation of drops in rabbit eyes.

Table 3 presents the results of cholinesterase assays in dog blood serum and red blood cell fraction. Inhibition of cholinesterase activity to levels as low as 40 percent of normal were found in serum, while the lowest level in red blood cell activity was 64 percent, with two of the animals showing only slight inhibition to levels of 84 and 96 percent, respectively. According to Hawkins and Mendel, 56 percent of the cholinesterase in rabbit serum is "pseudocholinesterase," and since this esterase is more readily inhibited than "true" or "specific" cholinesterase, this would explain the lower levels of cholinesterase activity. According to Koelle and Gilman,[21] dog serum cholinesterase is much more sensitive to DFP, and for this reason is more readily inhibited.

Table 4 presents the results of cholinesterase assays in human serum, and levels as low as zero were found. There was little or no change in red blood cell cholinesterase activity in human blood, in all samples assayed.

Koelle and Gilman[21] were able to demonstrate that in the rat, the brain and muscle esterases are considerably more sensitive to DFP than is the enzyme of the red blood cells. In the rabbit, the same type of activity is present, and brain cholinesterase was inhibited to much lower levels (25 percent) than the red blood cell cholinesterase (63 percent). In salivary gland, the esterase activity was reduced to 55 percent and in ileum to 36 percent after 28 days of exposure to coralox by instillation of eyedrops. Co-Ral, which must be activated in the liver by oxi-

TABLE 2

EFFECT OF CORALOX ON CHOLINESTERASE ACTIVITY IN TISSUES OF THE RABBIT

Tissue	Cholinesterase Activity*									
	No. Rabbits	Normal	Mean Deviation	7 Days Treatment	Mean Deviation	14 Days Treatment	Mean Deviation	28 Days Treatment	Mean Deviation	Percent of Normal
Brain	4	44.8	±12.1	32.50	±5.1	11.82	±6.6	11.22	± 2.4	25.0
Salivary Gland	4	37.2	± 3.3	15.73	±3.7	14.30	±7.2	20.52	± 4.3	55.0
Ileum	4	32.9	± 8.2	18.4	±2.8	12.00	±5.1	13.51	±10.2	36.0

* Expressed as cmm. CO_2 liberated per 50 mg. wet tissue per 10 min.

TABLE 3

CHOLINESTERASE ACTIVITY IN DOG BLOOD TREATED WITH 0.25-PERCENT CORALOX AS EYEDROPS

	Cholinesterase Activity*					
	Dog No. 1		Dog No. 2		Dog No. 3	
Days of Treatment	Serum	Red Blood Cells	Serum	Red Blood Cells	Serum	Red Blood Cells
Control	26.73	34.85	12.53	33.87	18.6	23.43
7 Days	12.04	27.82	10.29	21.12	8.17	21.76
14 Days	16.46	34.54	8.18	28.85	4.94	14.30
28 Days	12.03	28.59	8.93	21.81	7.05	22.42

* Expressed as cmm. CO_2 per 0.1 ml. per 5 min.

dation, was able to inhibit the cholinesterase activity in the blood to levels of 70 percent of normal after one week's instillation as eyedrops.

Mazur and Bodansky[17] have shown that in the monkey, the brain, serum and red blood cell esterases are comparable to those in humans, and that the inhibition of serum cholinesterase by DFP was greater than that of red blood cell cholinesterase. Results of this study in humans indicated that serum cholinesterase is very sensitive to coralox, while the true cholinesterase of human red blood cells was little affected.

Return of cholinesterase activity in rabbits was found to occur to 98 percent of normal in serum and to 80 percent of normal in red blood cells in 18 days.

No evidence of toxicity, such as muscarinic twitching, salivation, diarrhea or loss of appetite, was noted in any animals or humans studied.

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TABLE 4

CHOLINESTERASE ACTIVITY IN HUMAN SERUM ON TREATMENT WITH CORALOX FOR CONTROL OF GLAUCOMA

Weeks of Treatment	Cholinesterase Activity in Serum*		
	Males	Females	Values at Beginning of Treatment
	Normal = 32.2 ± 1.3*	25.69 ± 4.5*	(physostigmine-pilocarpine)
1	22.36		
2	24.70		19.30
8	2.85	15.91	25.40
	21.36		26.32
	5.00		
12	6.22	1.0	21.84
		5.83	9.2
		3.24	
		10.35	26.02
16	4.4		15.15
	9.19		
20		6.01	15.8
32		13.4	19.24
		5.2	
		5.89	
		6.70	24.37

* Normal values: Male: 32.2 ± 1.3 cmm. CO_2 per 0.1 ml. per 5 min. Female: 25.69 ± 4.5 cmm. CO_2 per 0.1 ml. per 5 min. (average of 10 values).

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A COMPARISON OF VISUOSENSORY AND VISUOMOTOR DISTURBANCES IN RIGHT AND LEFT HEMIPLEGICS*

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INTRODUCTION

Until the advent of World War I, visual disorientation was regarded mainly as a manifestation of visual agnosia. The investigation of cases of gunshot wounds of the brain during 1914-1918, however, showed that visual disturbances could occur without visual agnosia and homonymous hemianopia. After World War I, the British literature began to describe visual disorders in detail. Its main characteristics have been well summarized by Gordon Holmes[1] and more recently, by Russell Brain.[2] Both investigators have shown visual disorientation to be a defective localization of objects in space in the absence of visual object agnosia. The problem of visuosensory and visuomotor disturbances also has a prominent place in the German literature following World War I. Notable contributions were made by Kleist[3] who devised a classification of visual disorientation and

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by Poetzl[4] who grouped together the various spatial forms of agnosia. Karlin, et al.[5] recently compared intellectual and linguistic disturbances in right and left hemiplegic patients. Their findings indicated that the left hemiplegics were more seriously disturbed in these areas.

The hemiplegics, especially the majority of right hemiplegic patients, have aphasia—a disturbance in language function. On the other hand, the majority of the left hemiplegics appear to communicate well. Because of the difficulty in communication, the right hemiplegics appear to be more seriously disturbed than do the left hemiplegics. This paper was undertaken as part of a general study of right and left hemiplegic patients with and without aphasia. Specifically, this paper presents the results of an investigation to determine whether hemiplegic patients show any impairment of visual processes, and if any differences in visual functioning exist between the right and left hemiplegics.

Methods and Materials

The subjects in this study consisted of 16 right and 12 left institutionalized hemiplegic patients. The right hemiplegics were between the ages of 43 to 78 years, while the left hemiplegics were 37 to 75 years of age. The median ages were 58 years for the right hemiplegics, and 64.5 years for the left hemiplegics. The patients in each group were matched as closely as possible with regard to chronologic age, and number of years of formal academic education.

The following tests were administered to each patient: central and peripheral visual fields, the performance scale of the Wechsler adult intelligence scale (Wais),[6] tests of visual agnosia on the Eisenson examining for aphasia,[7] and the Bender gestalt test.[8]

In testing for central field defects, the patient was seated one meter away from a tangent screen receiving seven foot-candles of illumination. The test object consisted of the smallest white mm. test object perceived by the patient. In the peripheral field examination, the patient was seated in front of a standard perimeter, at the usual distance of one third of a meter. Three-mm. test objects were used.

In the psychologic evaluation, the intratest performance scores obtained for the two groups on the Wechsler scale, were compared for any significant differences. In the administration of tests for visual agnosia, the subject was asked to do one of the following: name the item pictured; point to the item when named by the examiner; match the item indicated by the examiner with one on the opposite page; or select the name from among several given orally by the examiner. In administering the Bender gestalt, every patient was requested to copy the designs according to standard procedures.[8] Instead of using the scoring system as given in Pascal and Suttell,[9] it was decided to utilize five ratings of disturbance: none, slight, moderate, severe, and complete.

Results

Concerning central and peripheral visual field disturbances, initial investigations immediately following the onset of the cerebrovascular accidents, demonstrated homonymous hemianopia in the majority of cases. Six months later, out of 16 right hemiplegics, 10 of whom had aphasia, none demonstrated a homonymous hemianopia. On the other hand, in testing 12 left hemiplegics, all of whom were without aphasia, three were found to have a left homonymous hemianopia.

Both groups of hemiplegic patients did poorly on the performance scale of the Wechsler scale (table 1). The digit symbol subtest which involved visual acuity, motor co-ordination, and speed, was found to be most difficult by each group. In a further comparison of all the subtests of the Wechsler scale, the left hemiplegic patients showed lower scores than the right hemiplegics. Our findings are in agreement with those of Anderson[10] who indicated that cases with domi-

TABLE 1

A COMPARISON OF MEDIAN SCALE SCORES OF TWO GROUPS OF HEMIPLEGIC PATIENTS ON THE PERFORMANCE SCALE OF THE WECHSLER ADULT INTELLIGENCE SCALE

	Right Hemiplegia	Left Hemiplegia
	No. of Patients—16 Median Scale Score	No. of Patients—12 Median Scale Score
Performance Scale		
Digit symbol	1.0	0
Picture completion	3.5	2.0
Block design	4.0	3.0
Picture arrangement	3.0	0
Object assembly	3.5	2.0

nant hemisphere damage show a greater loss of verbal abilities, while the nondominant hemisphere cases show a greater loss in performance. Weisenberg and McBride,[11] also showed that right hemisphere damage (left hemiplegia) resulted in lower performance.

On the Eisenson examining for aphasia, three cases of the right hemiplegics demonstrated slight visual agnosia, as compared to the left hemiplegics who showed no disturbance in this area.

On the Bender gestalt, it was found that the left hemiplegic patients had a greater degree of disturbance than the right hemiplegics (table 2). While both groups showed evidence of disturbance, the findings agree with those of Wood,[12] who found that left hemiplegics showed a higher proportion of disturbance than did the right hemiplegics. Of special importance is the fact that none of the left hemiplegics were able to reproduce the designs correctly; whereas, five right hemiplegic patients were able to do so. The right hemiplegic patients were previously right handed and, as a result of their physical handicap, were unable to use the preferred right hand. All the left hemiplegics were also right handed. Yet, they had more difficulty in doing these tasks in spite of the fact that they did not have to change handedness. From an analysis of the Bender gestalt (table 2), one can see that the left hemiplegics all demonstrated slight to severe disturbance. None of the left hemiplegics obtained a perfect reproduction or a completely abnormal score. Contrary to this, the right hemiplegics produced scores in all five categories. In addition, more than one third of the right hemiplegics had either a complete disturbance or no disturbance whatsoever.

Discussion

Visuosensory and visuomotor disorientation are comprehensive descriptive terms covering a number of higher visual functions. In this paper, the component parts of visual disorientation were broken down and evaluated.

Concerning the visual fields, out of 28 patients examined soon after the onset of the cerebrovascular accident, a majority of both right and left hemiplegics demonstrated homonymous hemianopia. Subsequent examinations six months later, revealed only three cases of homonymous hemianopia in both groups. One must therefore postulate a spontaneous resolution of the hemianopic defect.

This study also demonstrated that very few problems of visual disturbance resulted from lesions of the afferent visual pathways, since only three cases of homonymous hemianopia in left hemiplegics were present, in the patients examined. Secondly, very few

TABLE 2

A COMPARISON OF DISTURBANCE BETWEEN TWO GROUPS OF HEMIPLEGIC PATIENTS IN THE BENDER VISUAL MOTOR GESTALT TEST

	Right Hemiplegia	Left Hemiplegia
	No. of Patients—16 (%)	No. of Patients—12 (%)
*Amount of Disturbance**		
None	29	0
Slight	23	33
Moderate	36	25
Severe	6	42
Complete	6	0

* Amount of disturbance consists of either distortion, rotation, or perseveration.

of the visual problems were due to visual agnosia, since only three right hemiplegic patients exhibited a slight deficiency in this area. Yet, in spite of these two negative findings, all of the patients showed severely impaired function when tested on the performance scale of the Wechsler scale and the Bender gestalt. One must therefore conclude that higher visual disorders are a result of damage to that integrative process in the brain in which visual perception evokes a normal act of performance. In a review of the literature, one cannot find any evidence concerning the exact position in the brain where these higher visual functions are integrated.

In comparing the right and left hemiplegics, it would appear that since right hemiplegics exhibit aphasia, they are more severely handicapped than the left hemiplegics. Left hemiplegics have been considered good prospects for rehabilitation, since they have no difficulty in comprehending instructions or expressing their needs. In this investigation, 10 in a total of 16 right hemiplegics had aphasia, while none of the 12 left hemiplegics had aphasia. However, in spite of being able to communicate well, this study has shown that when carefully screened, the left hemiplegic patients presented more visuosensory and visuomotor disturbance than did the right hemiplegics. The battery of tests used indicate that this is not the result of a central or a peripheral visual field defect or a visual agnosia. It is rather a fundamental disturbance in visuospatial discrimination. This is in agreement with Knapp[13] who has also shown that the left hemiplegics have more serious visual impairment than the right hemiplegics. The results of this study support Carroll's[14] premise that from a vocational point of view, the visuosensory and visuomotor deficits of the left hemiplegic patients, although less obvious, may actually present greater problems in rehabilitation than in the right hemiplegics with aphasia.

Summary

The purpose of this study was to compare a group of right hemiplegics with a group of left hemiplegics to determine if visuosensory and visuomotor disturbances existed, and to what extent they differed in each group. Both groups showed disturbance in performance items of the Wechsler scale, and on the Bender gestalt. However, the left hemiplegics demonstrated more disturbances in visuospatial discrimination, in spite of little visual agnosia, only three cases of homonymous hemianopia, and no language dysfunction as indicated by no aphasia. It is also suggested that, if carefully examined, the left hemiplegic offers less chance of vocational rehabilitation than does the right hemiplegic with aphasia.

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CLINICAL APPLICATION OF GONIOSCOPIC FINDINGS TO EVALUATION OF GLAUCOMA OPERATIONS*

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The clinical evaluation of the prognosis after glaucoma operations is very valuable and relies upon the postoperative results of visual acuity, visual fields, and ocular tension. Gonioscopy is an important method not only in diagnosing glaucoma but also in assessing the prognosis after operation.

METHOD

After disinfecting the eye, the contact glass is inserted between the lids and fitted against the eyeball. Saline solution is used to remove the air bubbles in the space between the lens and the cornea. The contact glass is well centered upon the surface of the cornea and the angle is observed through the contact glass.

RESULTS

I. ACUTE INFLAMMATORY GLAUCOMA

Gonioscopically, 22 eyes showed narrow angles and peripheral anterior synechias. The method of operation consisted of a trephining operation in 14 eyes, Wheeler's operation in six and iridectomy in one. Wheeler's operation and Shoji's sclerectoiridectomy were repeated on each eye after trephination and Wheeler's operation.

After these operations, generally, the peripheral anterior synechias were detached from the trabeculae and the angle of the anterior chamber was partially widened. The iridectomy portion showed an open angle. Typical cases are:

CASE 1

Acute inflammatory glaucoma, right eye. The patient, a woman, aged 36 years, was first seen on August 31, 1952. She had had ocular pain and blurred vision in the right eye for one month. Without correction, her vision was 0.06 in the right eye and 0.8 in the left. Her ocular tension was 47 mm. Hg (Schiøtz) in the right eye and 27 mm. Hg in the left. Her right eye showed congestion, corneal edema, and nasal constriction in the peripheral field.

A trephining operation was performed on the right eye on September 2nd. The anterior chamber reformed early. The postoperative vision was 0.08 (0.2 with a —1.5D. sph.), ocular tension 30 mm. Hg, and the visual field was enlarged after 20 days.

About six years later, on January 11, 1959, her eyes were checked. A gonioscopic examination of the right eye showed that the area of iridectomy was open but the remaining angle was closed. However, the area of iridectomy was so small and the coefficient of out-flow so decreased (0.075 cu. mm./min./mm. Hg) that the vision dropped to hand movements, with the ocular tension rising to 51 mm. Hg.

CASE 2

Acute inflammatory glaucoma, left eye. The patient, a woman, aged 54 years, was first seen on November 1, 1957. She had visual disturbance and ocular pain in the left eye since October 29th. Her vision was 0.5 (1.0 with a —0.5D. sph.) in the right eye and 0.03 without correction in the left. The left eye showed hyperemia, corneal edema and a shallow chamber with ocular tension increased to 65 mm. Hg. A gonioscopic examination showed peripheral anterior synechia.

A trephining operation was done on this eye on November 5th. Postoperatively the angle was open at the area of iridectomy, nasal and lower angles. Uncorrected vision was 0.2 and the ocular tension 26 mm. Hg.

The gonioscopic finding about two years later was unchanged. Visual functions were being well maintained. Vision remained stationary; ocular tension

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was 23 mm. Hg, and the C value 0.25 cu. mm./min./mm. Hg with a slightly enlarged visual field.

CASE 3

Inflammatory glaucoma, right eye. The patient, a woman, aged 59 years, was first seen on December 24, 1959. She had pain, visual disturbance in the right eye and vomiting for three days. Vision was hand movements in the right eye and 0.3 (0.5 with a −2.0D. sph.) in the left. Ocular tension was 51 mm. Hg, the C value 0.04 cu. mm./min./mm. Hg and the angle closed. On December 29th, a trephining operation was performed on the right eye.

A postoperative gonioscopic examination revealed an open small portion of foramen at the coloboma iridis with a closed angle at the remaining portion. The ocular tension was 37 mm. Hg and the C value remained 0.16 cu. mm./min./mm. Hg. At reoperation, Wheeler's operation was employed on the temporal side of this eye on February 25, 1959. The angle was wide open postoperatively at the temporal side and at the coloboma iridis. The visual function was improved, the vision became 0.05 (0.06 with a −8.0D. sph.), the ocular tension 20 mm. Hg and the C value 0.24 cu. mm./min./mm. Hg, with an enlarged visual field.

CASE 4

Bilateral acute inflammatory glaucoma. The patient, a woman, aged 58 years, was first seen on March 31, 1959. She had had pain in both eyes for 10 days. The vision was hand movements and the ocular tension 55 mm. Hg. Gonioscopically peripheral anterior synechia was present. On April 2nd, Wheeler's operation was performed on both eyes at the same time.

The postoperative gonioscopic findings on April 23rd showed that there was an open angle at the coloboma iridis and the temporal side of the right eye. In the left eye, the upper angle revealed a small coloboma iridis with the angle completely closed. The vision improved to 0.1 (0.2 with a +3.0D. sph.) in the right eye and 0.05 (0.1 with a +3.5D. sph.) in the left. The ocular tension dropped to 5.3 mm. Hg in the right eye and 23 mm. Hg in the left. The C value also improved to 0.23 cu. mm./min./mm. Hg in the right eye but was disturbed in the left, 0.09 cu. mm./min./mm. Hg. On May 19th, Shoji's sclerecto-iridectomy was performed on the left eye.

The postoperative gonioscopic examination of the left eye showed an open and wide angle on the upper side. Vision of the left eye improved to 0.06 (0.2 with a +3.5D. sph.), ocular tension, 10 mm. Hg and C value 0.29 cu. mm./min./mm.Hg.

II. CHRONIC INFLAMMATORY GLAUCOMA

The preoperative gonioscopic finding in five eyes with chronic inflammatory glaucoma showed peripheral anterior synechias or scattered conical or trabecular synechias. Surgery consisted of a trephining operation in four eyes and Shoji's sclerecto-iridectomy in one eye. Wheeler's operation was used in one of the trephined eyes as reoperative procedure. After these operations, gonioscopy showed a wider angle and an open area at the coloboma iridis.

CASE 5

Chronic inflammatory glaucoma, right eye. A man, aged 40 years, was first seen on May 23, 1957. He had had visual disturbance of the right eye for about six years. Without correction vision was 0.06 and there was glaucomatous cupping of the disc and central constriction of the visual field of the right eye. Ocular tension was 29 mm. Hg and the C value 0.05 cu. mm./min./mm. Hg. Before the trephining operation which was performed on June 6, 1957, gonioscopy revealed a closed angle.

Postoperative gonioscopy showed a wide angle at the coloboma iridis and a narrowness of the other portion of the angle. At that time, uncorrected vision was 0.1, ocular tension 26 mm. Hg, and the C value 0.17 cu. mm./min./mm. Hg. About one and a half years later, the area of the coloboma iridis was still open and the condition of the eye was completely stationary.

CASE 6

Chronic inflammatory glaucoma, right eye. A woman, aged 33 years, had blurred vision and haloes in the right eye for one month. Vision in this eye dropped to 0.2 (0.8 with a −1.5D. sph.), the ocular tension was 45 mm. Hg and the C value 0.015 cu. mm./min./mm. Hg. The gonioscopic findings showed atrophic and scattered pectinate ligaments with a wide angle.

A trephining operation was done on January 13, 1959. After the operation there was a wide angle in the region of the coloboma and trabecular synechias in the remaining portion, especially nasally and temporally. The C value showed 0.13 cu. mm./min./mm. Hg. Therefore, Wheeler's operation was performed on February 10th. After the operation the angle was open on the upper nasal and temporal side. Vision increased to 0.8 (0.9 with a −0.75D. sph.), the oculuar tension decreased to 19 mm. Hg and the C value normalized at 0.23 cu. mm./min./mm. Hg.

III. SIMPLE GLAUCOMA

Gonioscopically, 21 eyes with simple glaucoma revealed wide angles. The operations consisted of trephining operations in 12 eyes, cyclodialysis in nine and Wheeler's operation in one of the trephined eyes. The chief gonioscopic findings in the eyes operated by trephining showed that there was no adhesion in the area of iridectomy and an open angle in the remaining portion. There was only one eye in which a peripheral an-

terior synechia covered the whole angle postoperatively. After cyclodialysis, the entire angle was always opened completely. There were, however, three cases which revealed a white lineal cleft between the iris root and the scleral spur.

CASE 7

Bilateral simple glaucoma. A man, aged 48 years, first visited our clinic on December 19, 1958, suffering from blurred vision in both eyes for a few months. In the right eye uncorrected vision was 0.8, ocular tension 28 mm. Hg and the C value 0.17 cu. mm./min./mm. Hg; in the left, uncorrected vision was 0.7, ocular tension 30 mm. Hg and the C value 0.20 cu. mm./min./mm. Hg. The visual field in both eyes was constricted centrally and there was glaucomatous cupping of the discs. The gonioscopic examination showed a wide angle in both eyes.

A trephining operation was performed on the right eye on October 28th. Postoperatively gonioscopy showed that the area of the coloboma iridis was open but the coloboma was small. There was a peripheral anterior synechia along the whole angle. The ocular tension dropped to 16 mm. Hg but the C value was still slightly disturbed, showing 0.45 cu. mm./min./mm. Hg.

To increase the outflow a trephining operation was again performed on December 23rd. On January 23rd, the gonioscopic finding revealed an open angle on two sides of the coloboma iridis and detachment of the synechia at the nasal and temporal angles. The C value improved to 0.295 cu. mm./min./mm. Hg. Vision became 0.7 (1.0 with a —1.0D. sph.), the visual field was slightly enlarged and ocular tension decreased to 23 mm. Hg. A trephining operation was done on the left eye on November 18th.

After the operation the angle was open at the coloboma iridis and wide open in the remaining portion. The ocular tension became 23 mm. Hg and the C value improved to 0.39 cu. mm./min./mm. Hg. Vision was 0.6 (1.0 with a —1.5D. sph.) and the visual field was slightly enlarged.

CASE 8

Bilateral simple glaucoma. A man, aged 58 years, visited our clinic on March 31, 1958, with complaint of haziness in both eyes which had lasted for six months. Uncorrected vision was 0.5, ocular tension 24 mm. Hg, and the C value 0.20 cu. mm/min./mm. Hg in the right eye. In the left eye, uncorrected vision was 0.1, ocular tension 32 mm. Hg, and the C value 0.04 cu. mm./min./mm. Hg. Glaucomatous cuppings were present in both eyes. Cyclodialysis was performed on each eye on April 15th and 30th. Postoperative gonioscopy revealed a white lineal cleft between the root of the iris and the scleral spur. After operation, in the right eye, visual function improved, uncorrected vision became 0.6, ocular tension was 13 mm. Hg, and C value 0.25 cu. mm./min./mm. Hg. In the left eye, uncorrected vision was 0.4, ocular tension 11.5 mm. Hg, and the C value 0.25 cu. mm./min./mm. Hg. The visual fields were also enlarged.

IV. SECONDARY GLAUCOMA

The eight eyes with secondary glaucoma included four with recent or chronic iridocyclitis, two with aphakic glaucoma, one with subluxation of the lens and thrombosis of the retinal central vein. Iris bombé or partial trabecular synechias, due to iridocyclitis, had closed the angle in two eyes.

CASE 10

Secondary glaucoma induced by iridocyclitis, left eye. A woman, aged 64 years, was first seen on June 9, 1958, with a history of iridocyclitis of the left eye since the age of 18 years. She had suffered ocular pain for two days. This eye had iris bombé and a gonioscopically closed angle, the vision being zero and the ocular tension 55 mm. Hg. Transfixio iridis was done on June 9th. After operation, the gonioscopy revealed that the angle was reopened except at the lower side, two perforated colobomas on the lower portion of the iris, and no adhesion between the anterior chamber and the lens. The ocular tension improved to 16 mm. Hg and the C value 0.185 cu. mm./min./mm. Hg.

CASE 11

Secondary glaucoma induced by the subluxation of the lens, right eye. A man, aged 23 years, visited the out-patient clinic on March 28, 1958, after trauma to right eye on March 18th. Vision was 0.02 (0.2 with a —4.0D. sph.). Ocular tension was increased to 54 mm. Hg in the right eye. Gonioscopy revealed a wide angle. The equator of the subluxated lens was observed at the upper temporal region of the posterior chamber. On June 3rd, the lens was removed by iridectomy. Postoperatively, the angle was wide open but tension remained stationary at 45 mm. Hg, the C value 0.075 cu. mm./min./mm. Hg, and vision was counting fingers at 20 cm. (0.05 with a +10D. sph.).

CASE 12

Aphakic glaucoma, left eye. A woman, aged 67 years, was first seen on January 9, 1957. She had undergone extracapsular extraction of the lens on January 28, 1958, with discissions later. The vision improved to 0.02 (0.3 with a +10D. sph.), the ocular tension was 10 mm. Hg and the C value 0.25 cu. mm./min./mm. Hg, with an open angle. On May 22, 1958, the vision of this eye decreased to 0.01 (0.2 with a +8.0D. sph.). The cornea was slightly edematous, the ocular tension was 22 mm. Hg, and the C value 0.25 cu. mm./min./mm. Hg, with the angle closed. A trephining operation was performed on June 15, 1958.

After the operation, the angle was wide open, with coloboma iridis. Vision was 0.01 (0.3 with a +10D. sph.), the ocular tension was 15 mm. Hg,

and the C value 0.27 cu. mm./min./mm. Hg. However, there was a recurrence on February 13, 1959, and the angle was closed except in the area of the coloboma iridis. Wheeler's operation was performed on February 18, 1959. After the operation, the angle became wide open except at the lower side. Vision improved to 0.01 (0.4 with a +10D. sph.), the ocular tension was 11 mm. Hg, and the C value 0.13 cu. mm./min./mm. Hg.

Case 13

Glaucoma induced by thrombosis of the central retinal vein, right eye. The patient, a man, aged 32 years, was first seen on March 17, 1958. He had a sudden disturbance of vision of the right eye on March 5th. Uncorrected vision was 0.03. The right fundus showed a typical thrombosis of the central retinal vein. On June 17th, ocular tension was increased to 52 mm. Hg, the C value was decreased to 0.08 cu. mm./min./mm. Hg, and vision diminished to light perception. Gonioscopy showed that the posterior portion of trabecular meshwork was covered by an anterior synechia; the anterior chamber was deep. A trephining operation was performed on July 16th. Postoperatively, the angle was wide open at the iris coloboma. However, the operation produced no improvement. Ocular tension remained at 59 mm. Hg, the C value 0.10 cu. mm./min./mm. Hg, and the vision zero.

Discussion

A gonioscopic examination is usually used to establish a diagnosis of glaucoma but it is valuable in evaluating the postoperative prognosis.

In acute inflammatory glaucoma, peripheral anterior synechias were observed pre- and postoperatively. When the size of the iris coloboma after the trephining operation was too small, as in Cases 1, 3, and 4, and the C value was obviously disturbed, the prognosis was less encouraging. This would seem to indicate that the prognosis in closed-angle glaucoma might be based on the extent of the increase in the width of the angle formed by the glaucoma operation.

In simple and chronic inflammatory glaucoma where the angles were open before the trephining operation and peripheral anterior synechias were induced by operation, the C values were also diminished. From these facts it seems that the prognosis for these eyes would parallel that of Case 1. In such cases the closed angle must be reopened so that the C value may be improved, as in Cases 3, 4, 6 and 7.

Occasionally, the wide angle of a glaucomatous eye becomes a closed angle after the operation, with the C value diminishing. To diagnose these postoperative obstructions of the angle gonioscopic examination is needed after the glaucoma operation. Postoperative anterior synechias may be induced by continuous contact between the iris root and the trabeculae, due to delayed reformation of the anterior chamber and a mild iridocyclitis after operation (Meyer).

Troncoso and Sugar reported that the prognosis in glaucoma was not related to peripheral anterior synechias of the iris over the entire angle. However, it would appear that their opinion is not correct. The presence of goniosynechias produces findings similar to those of closed-angle glaucoma and in these cases the decrease of the C value can be verified by tonography. For eyes having such goniosynechia, wide iridectomy or the cyclodialysis of Wheeler's operation is invariably needed to improve the C value.

Cases 11 and 13 (secondary glaucoma) showed gonioscopically that a considerably wider angle was produced by iridectomy but that vision and C values were not improved after the operation. It would seem that these two eyes could be classified as having malignant glaucoma since they showed a resistance to any kind of glaucoma operation. In these cases, one should not rely solely on the breadth of the wide angle.

Control of ocular tension does not depend upon a mechanical regulator only. However, since the angle of the anterior chamber is most important to the passage of aqueous humor, gonioscopy should be used to evaluate the condition of the angle after a glaucoma operation.

Summary

Evaluation of the prognosis after glaucoma operations from the standpoint of gonioscopic findings showed that:

When the extent of a wide angle is restricted or a wide angle before the operation

changes into a closed angle after operation, reoperation is necessary to open the angle at the earliest date so that the C value may be improved. It is emphasized that gonioscopy and tonography are valuable in the clinical evaluation of glaucoma operations.

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PTERYGIUM: ITS INCIDENCE, HEREDITY AND ETIOLOGY*

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Pterygia are frequently observed in tropical and subtropical countries. In Europe pterygia are seen more frequently on the eastern shores of the Mediterranean than in the northern countries. They are rare in England (Duke-Elder[1]). The tables compiled by Sous[2] and cited by Poncet[3] give the incidence of pterygia in Europe for every 100 patients: Copenhagen, 0.23; Glasgow, 0.22; Dublin, 0.27; Paris, 0.37; Lyons, 0.39; Naples, 0.38; Barcelona, 1.05; Cadiz, 1.87. Poncet[3] gives the following non-European data: Cuba, 2.54; Madeira, 10 percent of the population (Lawrence[4]); Borneo, Pontianak, most of the inhabitants between 30 and 40 years (Abrahams[5]).

I have observed that the inhabitants of the island of Aruba, an island lying about 20 miles off the north coast of Venezuela, are frequently affected with pterygia. To estimate the incidence of pterygium on the island of Aruba, a survey was made of 1,040 patients whose working and living kept them out of doors. These data are combined with those of Diponegoro and Mulock Houwer[6] and Ringland Anderson[7] in Table 1.

Because the average daily sunshine in tropical and subtropical countries is higher than in northern countries, several authors have suggested a correlation between solar radiation and the etiology of pterygium. Diponegoro and Mulock Houwer[6] and Kerkenezov[19] could prove that exposure to open air caused a predisposition to pterygium formation. The former authors believed in the etiologic importance of solar, infrared radiation (reflected radiation from the soil more than direct), while Kerkenezov[19] was of the opinion that exposure to the ultraviolet band of the solar spectrum was the etiologic factor.

In order to find out whether there was any correlation between the incidence of pterygium and such factors as outdoor and indoor work (exposure to sunshine), sex, race and Aruban origin, the 1,040 "outdoor" patients were classified in four main groups: (1) Arubans, Negroid* (AN); (2) Arubans, non-Negroid (AN̄); (3) non-Arubans, Negroid (Ā N); (4) non-Arubans, non-Negroid (Ā N̄).

Each of these main groups was subdivided by sex and the subgroups were classified according to whether work was done indoors or outdoors (fig. 1).

From the material, the following conclusions could be drawn:

1. Men working outdoors are more often affected than those working indoors. This could only be established for male patients

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* For this purpose an Aruban was defined as a person born on this island whose parents had also been born there; a non-Aruban, one born elsewhere of parents who had also been born elsewhere. A person whose outward appearance revealed his African origin was considered as Negroid.

TABLE 1

STATISTICS ON PTERYGIA

Country	Author	Year	Patients Examined	Pterygium (percent)
Cuba	Lopez[8]	1814	—	9
Spain	Fernandez[9]	1874	1,000	4.7
Greece	Bistis[10,11]	1926	3,000	0.5
England	Gibson[12]	1927	36,000	0
Brazil	Alvaro[13]	1932	18,539	4.9
Russia	Ponomareff[14]	1933	5,328 males	
			600 females	8.6
Indonesia	Diponegoro,[6] Mulock Houwer	1936	Europeans:	
			1,455 males	2.3
			1,050 females	0.4
			Chinese:	
			1,740 males	4.1
			868 females	1.7
			Indonesians:	
			13,282 males	6.1
			5,316 females	4.3
Venezuela (Island of Margarita)	Grom[15]	1952	—	3
Australia (North West)	Ida Mann[16]	1953	2,866	4
(Alice Springs)	Welton[17]	1954	Aborigines	almost 50
(Orange, New South Wales)	Redmond[18]	1956	6,000	3.4
(Lismore, New South Wales)	Kerkenezov[19]	1956	3,000	
			males	12.7
			females	6.4
Netherlands Antilles				
(Aruba)	Hilgers[20]	1959	1,040	
			575 Arubans	28
			465 non-Arubans	17

because none of the women worked outdoors.

The following technique was employed: in the four main groups (AN, $A\overline{N}$, $\overline{A}$ N, $\overline{A}$ $\overline{N}$) outdoor males were compared with indoor males. The H_0 hypothesis

$$\sum_{\lambda=1}^{4} (p_\lambda{}^i - p_\lambda{}^0) = 0$$

was tested against the alternative hypothesis

$$\sum_{\lambda=1}^{4} (p_\lambda{}^i - p_\lambda{}^0) < 0; \quad p_\lambda{}^0 \text{ and } p_\lambda{}^i$$

(in which $\lambda = 1, 2, 3, 4$) are the respective chances for being affected in the λ's outdoor group and λ's indoor group. H_0 had to be rejected at the one-percent level in favor of

$$\sum_{\lambda=1}^{4} (p_\lambda{}^i - p_\lambda{}^0) < 0.$$

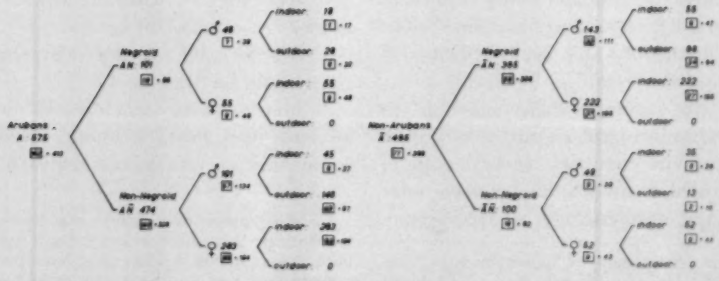

Fig. 1 (Hilgers). Correlation between incidence of pterygium, outdoor or indoor work, sex, race, and Aruban origin. □ indicates the number of persons affected by pterygium.

2. Males and females who worked indoors were equally affected. The same technique was used and in every group the males who worked indoors were compared with females who worked indoors. The H_0 hypothesis

$$\sum_{\lambda=1}^{4} (p_\lambda^m - p_\lambda^f) = 0$$

could not be rejected; p_λ^m and p_λ^f are the respective chances for being affected in the λ's male group and in the λ's female group.

3-A. The indoor workers (males and females) in the Aruban non-Negroid group (AN) were more often affected than the indoor workers in the other three groups. In this case Doornbos'[21] slippage test was used. The probability of exceeding was $<1\%$.

3 B. There was no difference in the incidence of pterygium between the outdoor workers of the Aruban, non-Negroid group ($A\overline{N}$) and the outdoor workers of the other three groups. These groups of outdoor workers consisted only of males because none of the females worked outdoors.

Summarizing the results of this statistical analysis, it may be stated that outdoor workers have a higher incidence of pterygium than indoor workers. The incidence of pterygium is the same for both males and females working indoors. Pterygia are more frequent in Aruban, non-Negroid males and females working indoors.

This could not be established for the Aruban, non-Negroid males working outdoors, possibly because this group is too small. However, the impression persists that this group (Aruban, non-Negroid males working outdoors) is also more affected. The observation that the Aruban, non-Negroid population is more affected than any other group makes the presence of an endogenous factor predisposing for pterygium likely. Such an endogenous factor might be a hereditary predisposition.

The relation between the incidence of pterygia and age groups of inhabitants of the island of Aruba is depicted in Figure 2 which shows that pterygia increase in direct ratio to age, and reach their peak in the age group of 60 years and older. An increased tendency to develop pterygia is also noted in the 40- to 49-year age group.

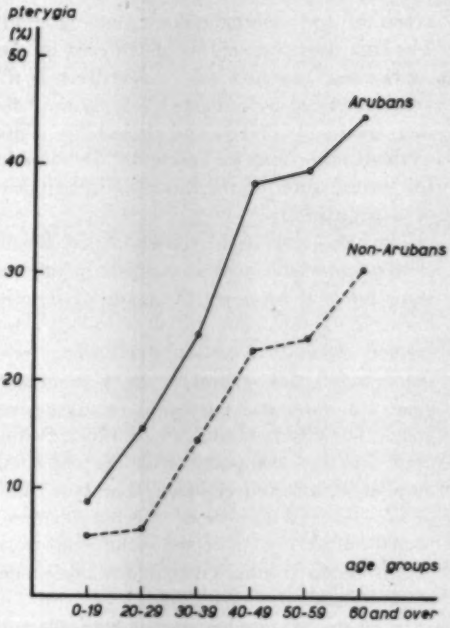

Fig. 2 (Hilgers). Incidence of pterygia for age groups.

Heredity

An early report concerning the hereditary factor in this condition was published by Armaignac.[22] The textbooks of Waardenburg[23] and François[24] cite the findings of Gutierrez-Ponce,[25] and Newman.[26] Recent publications are those of Enroth,[27] Kerkenezov,[19] and Komai[28] in Japan.

As mentioned before, the high incidence of pterygium in the non-Negroid Aruban population may possibly be explained by a hereditary factor.

I collected 17 non-Negroid Aruban families and tabulated the occurrence of pterygium in each family. The youngest child was aged 15 years; all children were living and

available for ophthalmologic examination. The data thus obtained were analyzed by the "aprioristic method of Apert-Bernstein" (recommended by Sanders[29]) or by the "direct method" (Neel and Schull[30]). This method, according to Sanders,[29] is suitable for examination of the mode of inheritance of a population.

The principle underlying Apert-Bernstein's aprioristic method consists in the assumption that whatever the mode of inheritance, it is the same in all families. The method assumes a certain mode of inheritance based, for example, on a dominant gene, a monorecessive gene, or two recessive genes. The observed number of affected children are then compared with the expected number of affected children. The best "fit" of the observed number of affected to an expected number of affected belonging to a certain mode of inheritance makes that mode of inheritance the most likely.

In all the 17 families one or both eyes of at least one parent was affected with pterygium. The total number of children was 75; the total number of children affected with pterygium was 44. Families with only one child were omitted because variance* in such families is zero. The conditionally expected numbers of affected children, if at least one child is affected, can be calculated with the formula:

$$w = \frac{ps}{1-q^s}$$

in which s is the total number of children in one family, p the expected probability of affected children and q the expected probability of normal children. For a dominant mode of inheritance p is likely to be ½; for a monorecessive mode of inheritance p is ¼; while for a two recessive mode of inheritance, p is likely to be 1/16.

In Table 2 the Apert-Bernstein method is applied to these data; computations were made for the assumption of two possible modes of inheritance, a dominant mode with p = ½ and a monorecessive mode with p = ¼.

The observed total number of affected was 44; the total number of expected for a dominant mode of inheritance or p = ½ is 39.8; the total number of expected for a monorecessive mode of inheritance or p = ¼, is 26.3. The standard deviation for p = ½ is 3.9; for p = ¼, 2.9.*

The difference between the observed number 44 and the expected number 39.8 is less than twice the standard deviation, which is a non-significant deviation for p = ½. For p = ¼ in contrast there is a significant deviation: the difference between the observed 44 and the expected number 26.3 is more than three times the standard deviation.

It is therefore likely that the high incidence of pterygia in the non-Negroid population of the island of Aruba can be explained by a dominant mode of inheritance.

Pedigrees were compiled of two families, which showed distribution over four generations and the incidence of pingueculum is also noted. Vertical lines denote a pingueculum (figs. 3 and 4).

In the first generation of family M. both a 80-year-old man and 70-year-old woman had pterygia; their three daughters, aged 52, 48, and 42 years, all had pterygia. In the third generation, one child of the second daughter showed a pterygium; four children of the first daughter, three of the second

* The variance (Neel and Schull[30]) is obtained from the formula:

$$\sigma_s^2 = \frac{spq}{1-q^s} - \frac{s^2p^2q^2}{(1-q^s)^2}$$

in which s is the number of children; p the probability of affected children; q the probability of normal children.

* According to Neel and Schull[30] "the standard deviation of expected total number of affected is the square root of the total variance obtained by summing the separate variances for the various sizes of family as frequently as these sizes occur."

Standard deviation

for p = 1/2: $\sqrt{15.435} = 3.9$

for p = 1/4: $\sqrt{8.569} = 2.9$

TABLE 2

ANALYSIS OF DATA BY THE APERT-BERNSTEIN METHOD

Total No. Children	No. Families Examined	Expected No. Affected per Family		Total No. Affected Expected		Variance per Family		Variance	
s	n	w		n×w		σ_w^2		n×σ_w^2	
		$p=\frac{1}{3}$	$p=\frac{1}{4}$	$p=\frac{1}{3}$	$p=\frac{1}{4}$	$p=\frac{1}{3}$	$p=\frac{1}{4}$	$p=\frac{1}{3}$	$p=\frac{1}{4}$
2	1	1.333	1.143	1.333	1.143	0.222	0.122	0.222	0.122
3	5	1.715	1.297	8.575	6.485	0.490	0.263	2.450	1.315
4	4	2.134	1.463	8.536	5.852	0.782	0.420	3.128	1.680
5	2	2.581	1.640	5.162	3.280	1.082	0.592	2.164	1.184
6	3	3.047	1.825	9.141	5.476	1.379	0.776	4.137	2.328
7	2	3.527	2.020	7.054	4.040	1.667	0.970	3.334	1.940
Total	17			39.801	26.275			15.435	8.569

daughter and one child of the third daughter displayed pingueculas.

Members of the fourth generation were too young to show either pterygium or pinguеculum, the eldest being seven years of age. The incidence of pingueculum in this family is conspicuous.

The first generation couple of family D. were both deceased but the eldest daughter, who was 55 years of age, could remember clearly that her mother had gone to Curaçao (sister island of Aruba) for the operation of a pterygium; in those times there was no practising ophthalmologist on Aruba. Nothing concerning a pterygium was known about the father. The second generation consisted of five females and one male; four of the sisters and the brother had a pterygium. In the third generation, the eldest daughter had seven children of whom one male and one female had pterygia. The son of the second generation had three children of whom a 20-year-old son and a 19-year-old daughter had pterygia. In total, four persons of the third generation were affected. The fourth generation consisted of four children of whom the eldest was an 18-year-old girl, who was not affected; the other three children were too young for the presence of pterygium.

ETIOLOGY

No evidence can be found to support the theory of Arlt[31] that pterygium is the result of a corneal ulcer; nor that it is a tumor (Hasner Edlem von Artha,[32,33] Schreiter,[34] Redslob[35]); pathologic examination of pterygium does not warrant such a view (Fuchs,[36–39] Gerundo,[40] Friedenwald,[41] Duke-Elder[1]). Neither is there reason to believe that disturbances of the venous circulation of anterior ciliary veins (Winther,[42] von Hippel,[43] Storogeff[44]) or extrinsic eye muscles (Theobald[45]) or eyelids (Bond[46])

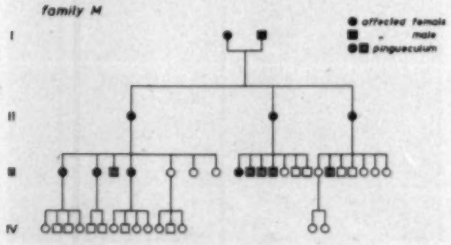

Fig. 3 (Hilgers). Pedigree of family.

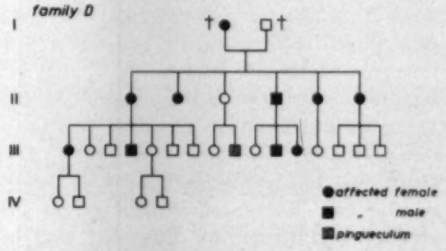

Fig. 4 (Hilgers). Pedigree of family.

or Stellwag von Carion's[47] corneal herpes or Poncet's[8] vibrions, have any etiologic importance.

Fuchs'[36] concept that damaging external influences (ausseren Schädlichkeiten) such as sun-glare, dust, wind, and heat are responsible for the formation of pterygium is generally accepted. In this connection the question arises: which of the many harmful open-air influences is responsible for the formation of pterygium? Elliot[48] believed in mechanical irritation by dust particles enhanced by the tear-flow from lateral to nasal. Rodriguez,[49] Dimitry,[50] Diponegoro and Mulock Houwer,[6] on the other hand, demonstrated that pterygia occur in dust-free areas. The last-named authors remarked that at sea there is little dust but pterygia occur among sailors.

Desiccation is a factor which Ringland Anderson[7] considered of etiologic importance. However, the high incidence of pterygia in areas with relatively high humidity, like the island of Aruba (average relative humidity 74 percent), and Kerkenezov's[19] data do not support this view. Nor is there reason to believe that persons exposed to heat, like stokers or furnace workers, develop pterygia as an occupational disease (Diponegoro and Mulock Houwer[6]). These authors observed a high incidence of pterygia in West-Java, Indonesia, where there is normally very little wind.

There is, in brief, no evidence to prove the etiologic effect of dust, wind, heat, or desiccation.

Contemporary opinion considers the action of sunlight of more etiologic importance. Diponegoro and Mulock Houwer[6] thought that the secondary, reflected radiation from the earth's surface are of etiologic importance because its wavelength lies between 8.0 and 12μ, that is, within the area of nonpenetrating infrared rays which are, therefore, absorbed by the superficial tissues of the eye. Kerkenezov[19] believed in the etiologic significance of ultraviolet rays of the solar spectrum. He supported his view by comparing the incidence of pterygia in areas with different concentrations of ultraviolet rays.

These writers could also show that pterygia occur more frequently in outdoor workers than in indoor workers. The fact that pterygia are observed more frequently in tropical and subtropical countries can also be attributed to prolonged exposure to solar radiation. The statistical analysis of the present study of 1,040 outdoor patients confirms the view that outdoor workers are more affected than indoor workers and that incidence of pterygia is not dependent on sex. However, hereditary predisposition plays a part in the formation of pterygium, probably through a dominant mode of inheritance. The hereditary predisposition may become manifest if an external influence favors development of the condition.

Some authors (Horner,[51] Fuchs,[36] Alt,[52] Kamel,[53] Kerkenezov,[19] Sugar and Kobernick[54]) see a close etiologic relationship between pterygium and pingueculum; others (Friede,[55] Duke-Elder[1]) deny this. The clinical observations of Kerkenezov[19] support the view that pinguecula can develop into pterygium. My observations agree with the view of those of the former authors (figs. 5, 6, 7 and 8). Similarity of pathology between pterygium and pingueculum was shown by Fuchs[37] and recently by Sugar and Kobernick[54] and Hilgers.[20] Degeneration of tissue elements is the characteristic feature of the pathology of pterygium and pinguec-

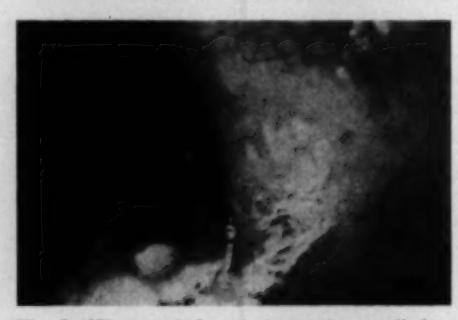

Fig. 5 (Hilgers). Inflamed pinguecula near limbus.

ula. Reviewing these data the question arises, how can progression of pterygium be explained?

Before answering this question, there are three points which should be considered: (1) the specific site at which the pterygium occurs; (2) the constitutional condition of the patient; (3) the fascicular corneal ulcer, a condition which may have some bearing on the problem of the progressive character of pterygium.

Pterygium originates at a site where two different kinds of epithelium, corneal and conjunctival tissue meet. It is known that at certain sites elsewhere in the human body where a similar meeting of tissues occur, abnormal conditions may arise. In gynecology, for example, cervical erosion; in dermatology, cancer of the lip.

In my opinion it seems likely that hereditary predisposition for pterygium exists in certain individuals. It is possible that the predisposition becomes manifest only when external influences are favorable. This assumption might explain the low incidence of pterygium in nontropical countries, as well as the clinical impression that pterygia regress in patients who have left the tropics for a more temperate climate.

Fascicular corneal ulcer in phlyctenular keratoconjunctivitis is a condition in which a limbal phlycten takes on an aggressive character and advances axially toward the center of the cornea. Its etiology is explained by allergic phenomena and the antigen in this condition is tuberculo-protein. Fascicular corneal ulcer and pterygium have several clinical characteristics in common:

1. They remain superficial and the cornea is never perforated.
2. They have a tendency to grow radially toward the center of the cornea.
3. Their progress seems to be connected with vessel proliferation and penetration.
4. They may recur.
5. Conjunctival eosinophilia is not present in phlyctenulosis (Theodore and Schlossman[56]); a similar observation was made by Hilgers.[20]
6. They destroy the transparency of the underlying corneal tissue.
7. They may become quiescent.

The conditions differ only in their location: fasciculus corneae occurs at any place

Fig. 7 (Hilgers). More extensive invasion of cornea. The connection with pinguecula is evident.

Fig. 6 (Hilgers). Earliest phase in development of a pterygium. The limbus is crossed and a small outcrop of white tissue penetrates the cornea.

Fig. 8 (Hilgers). The corneal epithelium is pushed up and forms a ridge ahead of the advancing, budding pterygium.

on the limbus; pterygium only nasally and temporally on the cornea. This difference in localization might be explained by the fact that in fascicular ulcer the antigen is endogenous and present in the bloodstream, while in pterygium (see later) the antigen is formed locally and is so present.

Schieck[57] explained the formation of phlyctens by assuming that minute amounts of specific antigen remained in the sensitized cornea and set off a purely local allergic reaction. Breebaart and James-Witte[58] could prove that (1) interaction between antigen and antibody may be purely local in character outside the vessel wall and of low intensity, and (2) that there is a direct relationship between available antigen and the subsequent allergic reaction. While phlyctenular corneal ulcer may develop within a couple of days, it may take years for the development of a pterygium.

If we return now to the question—how is progression explained—it is suggested that prolonged exposure to solar radiation causes proteins to become transformed into altered or denatured proteins. From the pathology of pterygium it is known that degenerative tissue elements are present; this material may act as foreign bodies but the process already mentioned may also occur. According to Theodore and Schlossman,[56] most antigens are proteins of complex biologic material. Antibody formation, as a reaction of the altered proteins acting as sensitizing substances or antigens, may occur and a subsequent interaction between antigen and antibody will result in allergic phenomena. In ophthalmology there is an analogous condition —endophthalmitis phacoanaphylactica, which occurs in individuals sensitized to their own lens protein. Burky[59] suggested that hypersensitivity to lens substance can be produced by the intermediary action of staphylococcus toxin. These triggering mechanisms are also known in phlyctenulosis (Theodore and Schlossman[56]).

The events leading to formation of pterygium may be somewhat as follows:

The prolonged exposure of superficial ocular tissues in the palpebral fissure to solar radiation causes degenerative tissue changes. These protein formations may act as foreign bodies but altered proteins may also be formed which act as antigens. The subsequent interaction of antigen and antibody produces an allergic reaction. In later stages the allergic reactions may increase in intensity, either as a result of increased antigen formation by prolonged exposure or as a result of superimposed infections. As a result of these processes combined with the specific site of the pterygium, and in some cases a hereditary factor, a pterygium may result.

The question—how is progression explained—may be answered thus: progression is the result of allergic inflammatory processes probably also triggered by superimposed infection. If a pinguecula is present in the palpebral fissure, it may be assumed that this degenerative condition will favor the formation of pterygium.

Conclusion

A statistical analysis of 1,040 "outdoor" patients confirms the view already expressed in the literature that outdoor workers are more affected than indoor workers. Not yet published is the fact that males and females working indoors are equally affected, which makes it likely that sex is unimportant in the incidence of pterygium.

In a certain number of families a dominant mode of inheritance of pterygium may be present. This assumption, however, does not mean that every pterygium occurs as the result of hereditary factors. Pterygium can also originate as an acquired pathologic condition excited by external factors. It seems possible that the hereditary disposition for pterygia will only become manifest if there are exogenous circumstances which favor its growth.

Degenerative tissue material of pterygium may act as a foreign body but exposure to solar radiation may lead to the formation of altered or denatured proteins which act as

antigens. These allergic inflammatory processes, probably also triggered by superimposed infections, may result in progression of the pterygium.

The etiology of pterygium is further connected with its specific site at the border of two kinds of epithelium as well as with a hereditary predisposition for its formation.

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EPIPHORA*

As the initial manifestation of a malignant nasopharyngeal tumor

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General and ophthalmic pathology textbooks frequently emphasize secondary involvement of the lacrimal sac by tumors originating in the nasopharynx or sinuses. Spaeth[1] mentioned these statements but asserted that he had never observed a secondary tumor of the lacrimal sac, although, of course, obstruction of the lacrimal drainage system in extensive neoplastic invasion of the orbit is not uncommon. A patient who had epiphora as the initial symptom of a histologically proven primary epidermoid carcinoma of the nasopharynx was recently referred to this Branch. Surgical exploration demonstrated that the tumor had involved the lacrimal sac.

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Case history

R.B.N. 00-82-61. This 53-year-old white seaman first noted epiphora on the right in the late summer of 1957, and a short time later (he did not recall how long) he felt a mass under the right side of his lower jaw. In the next few weeks he had a decrease in hearing in the right ear which was associated with a "popping sound," a painless swelling in the region of the right lacrimal sac, and slight pain on swallowing liquids.

He was first seen at the U.S. Public Health Service Hospital in New Orleans on January 24, 1958, with the presenting complaint of the mass beneath his jaw. The otolaryngologic examination revealed a firm nontender, submandibular mass measuring four centimeters in diameter; and a grayish-white, rough, friable tumor was found extending from the roof of the nasopharynx down the right pharyngeal wall around the eustachian tube and along the posterior pillar of the right tonsil.

On January 29th, a biopsy of this tumor was performed. Histologic study revealed large nests of anaplastic epithelial cells with poorly defined cytoplasmic limits and large, ovoid, hyperchromatic nuclei deep within the submucosal zone; the mucosal surface in one area had been broken by infiltrative cells of the same type and, in focal zones along the mucosa, the normal stratified squamous epithelium was replaced by markedly cellular areas

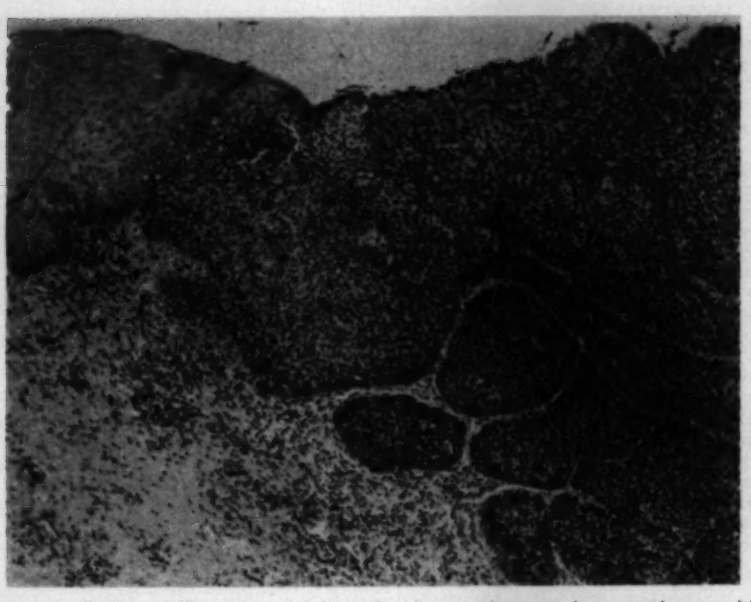

Fig. 1. (Cohan). Section of biopsy material from the pharyngeal tumor, demonstrating transition from normal epithelium to invasive epidermoid carcinoma. (Hematoxylin-eosin, ×80.)

containing hyperchromatic nuclei with anisocytosis, loss of polarity and numerous mitotic figures. The diagnosis was epidermoid carcinoma of the nasopharynx (fig. 1).

On February 19, 1958, the patient was transferred to the Radiation Branch of the National Cancer Institute. During the preceding three weeks he had had a dull aching along the lower orbital margin and over the right side of his face from the ear to the nose. Examination showed an extensive ulcerative neoplasm involving the whole of the right pharyngeal wall from the roof of the nasopharynx down to just above the level of the right vallecula and extending into the tonsillar region and soft palate on that side. In addition there were bilateral nodal metastases. Radiographs of the chest, thoracic, lumbar and cervical spine, pelvis, skull, all sinuses, and views of the hypopharynx and laminagrams of the larynx and of the base of the skull all failed to demonstrate signs of metastatic involvement or erosion of bone.

Because of the patient's complaint of epiphora and the finding of a swelling in the region of the right lacrimal sac, he was referred to our clinic on February 28th. His corrected visual acuity was 20/15 — 1, J1 on the right and 20/20 — 1, J1 on the left. The extraocular movements were full and the pupillary size and reactions normal. There was a slightly tender, hard mass medial and inferior to the right inner canthus measuring 13 by 10 mm.; it was slightly elevated but the skin over it was movable and not inflamed (fig. 2). Slitlamp and ophthalmoscopic examinations revealed no abnormalities. The intraocular pressure was 11 mm. Hg (Schiøtz) bilaterally. The lacrimal passages on the right could not be irrigated or probed because of the obstructing mass, but no material regurgitated from the puncta on attempted compression of the mass.

On March 20, 1958, a surgical exploration of the region of the right lacrimal sac was performed. After incising the skin, superficial fascia, and orbicularis muscle, a hard, gray-white mass with an irregular surface presented in the region of the right lacrimal fossa. It was freed up by blunt and sharp dissection laterally and nasally, where it

Fig. 2 (Cohan). Photograph of patient, demonstrating slight elevation just nasal and inferior to the right inner canthus with relative ironing out of the skin fold in this area.

overlapped the anterior lacrimal crest. The canaliculi were severed, and the cupola was dissected free. In reflecting the mass downward it was found to extend through a round defect in the bone of the lacrimal fossa about five millimeters in diameter, and into the right ethmoid sinus. It was separated from this extension and from its final attachment at the beginning of the bony lacrimal canal. The postoperative course was uneventful.

Gross examination of the specimen showed a firm, grayish, cone-shaped mass measuring 20 by 15 by 5.0 mm. Microscopically, a tumor filled the lacrimal sac and replaced its mucosa; it consisted of nests and cords of undifferentiated epithelial cells with indistinct cytoplasmic limits between strands of connective tissue. The tumor cells had pale blue cytoplasm and large, clear nuclei, which in some areas were lobulated, hyperchromatic, or in mitosis (fig. 3).

The patient completed his course of radiation therapy and was discharged from the hospital on June 23, 1958. He died on November 12, 1958, and the autopsy, performed at the U.S. Public Health Service Hospital in New Orleans, revealed metastases of the epidermoid carcinoma to lung, trachea, liver, esophagus, lymph nodes, and tongue; the ethmoid sinuses were not examined.

Comments

During the last century and the first years of this century, there was a growing recognition by European authors of the nasal, optic, cervical, and neuralgic symptoms and cranial nerve palsies produced by nasopharyngeal tumors.[2] In 1922, New[3] made a major contribution to the clinical awareness of these tumors by emphasizing that they are much more common than generally realized and that the striking lack of nasal or nasopharyngeal symptoms in many cases often results in mistaken diagnosis and treatment. Subsequently, several series of cases of nasopharyngeal tumors have been collected in which the symptom complex has been carefully documented. In reviewing approximately 1,800 cases, most of them from the largest of these series,[2-20] there was no mention of lacrimal sac involvement as an initial or early manifestation of the nasopharyngeal tumor.* The ophthalmologic literature pertaining to epiphora and diseases of the lacrimal apparatus over these same years was surveyed, and no case comparable to the one reported here was found.†

In his brief discussion of secondary tumors of the lacrimal sac Duke-Elder[22] includes malignant nasal epithelial tumors and gives one reference to a "typical" tumor of this type.[23‡] However, its rarity is emphasized by the fact that in his 18-page section devoted to a thorough review of the ophthalmic manifestations of nasopharyngeal tumors no mention is made of lacrimal sac involvement.

It has been observed that primary carcinomas of the nasopharynx and those of the lacrimal sac are "identical histologically and developmentally"[24] and they occur in these areas in approximately the same proportions.[2,24] Since the former frequently metastasize or extend from a minute or even undetected tumor,[8,25,26] some of the cases described as primary lacrimal sac tumors with extension into sinuses and nasopharynx might, initially, have been examples of secondary involvement of the sac by unrecognized neoplasms arising in the nasopharynx. This possibility would suggest that all cases of suspected lacrimal sac tumors should be carefully evaluated for a nasopharyngeal primary.

On the other hand, one might logically expect a stage in primary neoplasia of the lacrimal sac which precedes Spratt's[28] "first stage" (epiphora only) when a very small, asymptomatic tumor in the sac might extend and metastasize just as tumors which begin

* One patient (Schlivek's[8] Case 2) complained of epiphora but this was a late symptom, and there was no mention of obstruction of the lacrimal passages in the thorough ophthalmic examination; the patient had severe ocular pain from extension of the tumor into the skull, a Horner's syndrome, and seventh cranial nerve involvement.

† In his paper on exophthalmos in 1941 Reese[21] included one case of extension from a lesion in the nose "to orbit via tear sac," but since symptomatology was not dealt with, the stage of the disease in which this occurred was not specified.

‡ The clinical and histologic description of this tumor is most consistent with the diagnosis of a papilloma of the lacrimal sac or nasopharynx and so it is not comparable to the case presented here or those in the literature reviewed.

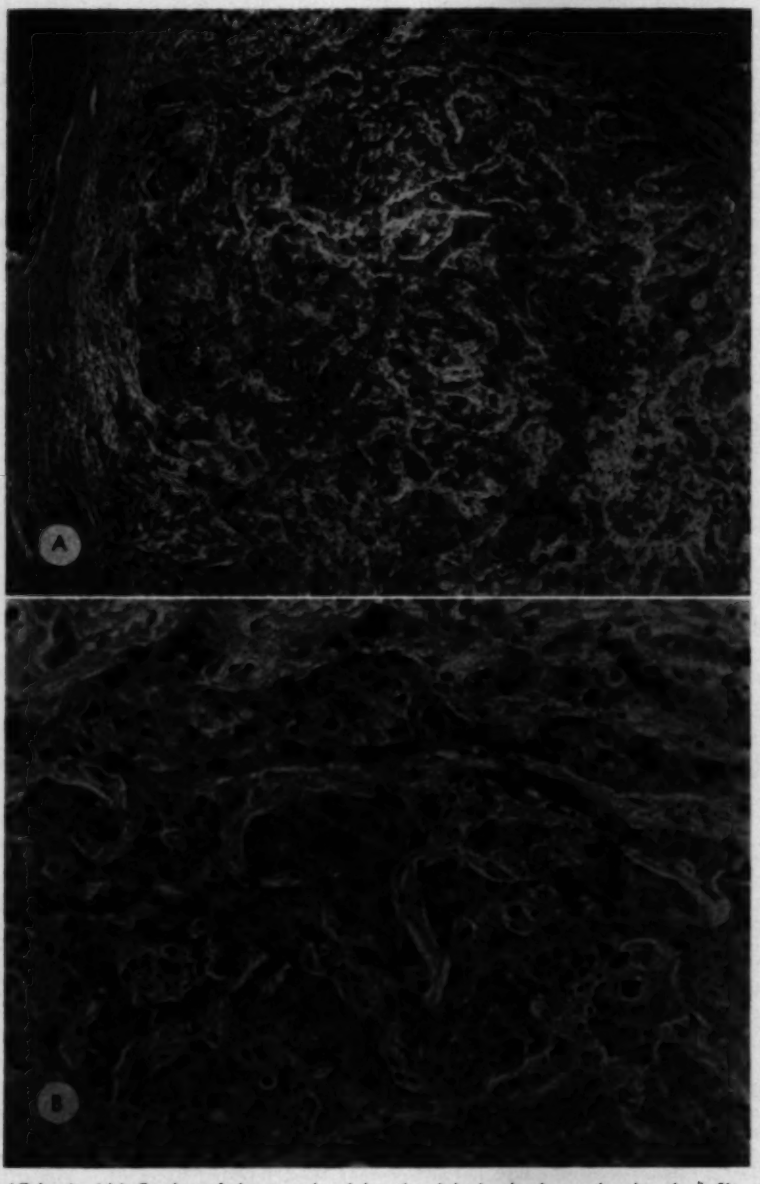

Fig. 3 (Cohan). (A) Section of the mass involving the right lacrimal sac, showing the infiltrating pattern of nests and cords of tumor cells within the connective tissue. (Hematoxylin-eosin, ×67.) (B) Higher power of the same section to demonstrate cytologic characteristics of the tumor cells. (Hematoxylin-eosin, ×205.)

in the nasopharynx so often do. If such cases do exist, when they extend into nasopharynx sinuses, orbit, skull, and nodes,[§] they might be misdiagnosed as carcinomas of nasopharyngeal origin. So perhaps the possibility of a minute primary tumor of the lacrimal sac should be considered in cases of cervical node or skull involvement in which no nasopharyngeal tumor is found.

Summary

1. A case has been presented in which epiphora was the initial symptom of a primary epidermoid carcinoma of the nasopharynx; subsequent surgical exploration demonstrated that the tumor had involved the lacrimal sac.

2. A review of approximately 1,800 cases of nasopharyngeal tumors reported in the literature from the point of view of symptomatology and of the pertinent ophthalmologic literature revealed no comparable case.

3. Early involvement of the lacrimal sac by nasopharyngeal carcinomas should be included in the differential diagnosis of epiphora and seriously considered in tumors of the sac, since some neoplasms thought to be primary in the sac might be instances of secondary involvement of it by a small nasopharyngeal tumor.

§ Both literature[1, 27] and textbook[22] emphasize these as the usual pathways of spread in primary lacrimal sac tumors.

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PRINCIPLES OF LENS DELIVERY*

WITH AND WITHOUT ALPHA CHYMOTRYPSIN

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The effectiveness of alpha chymotrypsin as a zonular lytic agent is now established and despite words of caution from responsible investigators it is gaining wide acceptance as a useful and invaluable aid in the management of patients with resistant zonular fibers.

Under ordinary circumstances it now seems apparent that there is really very little indication for the routine use of the enzyme, as the present methods of mechanical rupture of the zonule can usually be carried out without complications in the average patient over 60 years of age. When the indications for enzyme utilization are present, however (in younger age groups and in those with firm zonules), the surgeon in electing this method must realize that he is creating a completely different set of anatomic conditions and must adapt his technique of lens delivery to the altered circumstances. In effect he is lysing the zonule before the application of instruments, thus the actual instrumentation is carried out on a subluxated lens.

The best method of handling the lens under these changed conditions is, at present, open to question but can in part be answered by critically evaluating the mechanics of the various methods of lens delivery now commonly in use. The most effective method of dealing with an intact zonule may not be the best method with a prelysed zonule.

The controversial subject of sliding versus tumbling and the forceps versus the erisophake must now be re-evaluated by every surgeon who intends to use alpha chymotrypsin. Since conclusions must be based on individual experience, the thoughts expressed here are by no means absolute.

Prior to the introduction of alpha chymotrypsin the majority of cataract surgeons seemed to prefer the tumbling technique with capsule forceps. The reasons for this are numerous but probably of significance is the fact that the average surgeon feels more secure with this method. Because the principles of the technique are easy to explain and understand, it is often the first method taught during residency training. The technique, based on sound principles, can be easily mastered. Compared to the sliding technique with direct lysis of the zonule, it is a relatively blind procedure, but this makes the surgeon more relaxed because he does not have a chance to observe vitreous bulge and so-called vitreolenticular adhesions commonly seen when the sliding technique is used.

Usually all turns out well with the tumbling method, even in the hands of the inexperienced surgeon in training, so there is a tendency for him to stay with this method and gradually to perfect his technique. In the end he becomes highly skilled and often

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challenges anyone who suggests that some other method might be better.

The mechanics of the tumbling technique are too well known to discuss in detail but the advantages of the method and apparent safety are based on three factors:

1. The traction and counter pressure maneuvering are applied to the eye at an area farthest removed from the open wound.

2. The eye is maintained in a relatively closed position throughout most of the procedure, thus sealing off avenues of vitreous escape.

3. The above factors permit maximum amounts of traction and counter pressure to be applied in varying proportions depending on the need.

As soon as the zonule ruptures at the 6-o'clock position and the lower equator of the lens dislocates and rides up, the lens expressor is redirected to almost horizontal so that there is no longer any pressure against the vitreous body. The cornea is gradually tucked under the tumbling lens and maintains close contact with it throughout the procedure. The upward traction and rocking movements aided by pressure from the tucking maneuver cause the zonule to separate from the original rupture along both sides of the lens toward 12-o'clock position which, theoretically, should be the last portion of the zonule to remain attached. As the zonule gives way in this manner the lens is tumbled, with the upper zonular fibers being used as a hinge upon which to rotate it. As the uppermost zonular fibers are the last to separate, they also serve as an effective barrier against vitreous loss. The tucking of the cornea produces an arc of contact between the cornea and lens along its inferior surface and the tumbling equator of the lens maintains an arc of contact with the posterior surface of the cornea.

When properly executed the tumbling technique, although somewhat blind, is highly effective and safe for it sets up a series of barriers against vitreous loss that are dynamic in the sense that the various contact areas between lens and cornea move with the lens. One is able to take full advantage of both traction and counter pressure with minimum danger of vitreous spillage.

To coin a phrase, the tumbling technique might also be referred to as "the closed-eye technique." In contrast, the sliding procedure with direct stripping of the zonule might also be termed an "open-eye technique."

The sliding procedure has the advantage of being done under direct visualization but, since the initial rupture of the zonule occurs at the 12-o'clock position, one of the barriers against vitreous loss is immediately lost and the eye is left in a vulnerable position. In addition manipulations are carried out at the most open portion of the wound. The delivery depends mostly on traction, for even mild pressure from below will tend to produce a vitreous bulge between the lens and posterior scleral lip. When properly executed, however, the method can be very effective even with very resistant zonules.

It is possible to tease resistant zonular fibers away from the lens over the upper half of the equator but difficulty is encountered when the lower portion of the zonule tends to remain attached. Unless skillfully handled with rocking or torsional movements, the surgeon is often tempted to aid delivery by exerting pressure from below, rather than merely support, thus resulting in a large vitreous bulge or loss through the open wound.

Although the sliding method has many strong advocates, the margin of error seems to be less and the incidence of vitreous loss definitely higher. The late Dr. Daniel Kirby was, perhaps, the staunchest supporter of this method and he devoted considerable time to perfecting his own technique and to teaching others. Those who had an opportunity to observe and work with this master surgeon were truly impressed by his great skill with the sliding technique but, even in his hands, the loss of vitreous was not uncommon. When others attempted to duplicate

his methods, the results were often discouraging. In observing many other skilled surgeons employ the sliding technique, I have been impressed with the high incidence of vitreous bulge or loss.

Through these observations and from personal experience I have had opportunity to judge the relative merits of tumbling versus sliding and have long since concluded that the sliding technique in the presence of an intact zonule is definitely a dangerous method for the neophyte surgeon and occasional operator and should be reserved for the highly skilled and experienced surgeon who is not easily upset at the sight of a vitreous bulge and vitreolenticular adhesions nor particularly disturbed over actual loss.

Those who are not bothered by these complications and who enjoy the challenge and satisfaction of working against greater odds should not be discouraged, if their results compare favorably with tumbling statistics. In my opinion, however, those who are sufficiently skilled to keep the incidence of vitreous loss to one or two percent with the sliding method could reduce the incidence to almost zero by employing the tumbling technique.

The choice between forceps and the Bell erisophake should also be discussed. I have employed both instruments on many occasions but strongly favor forceps over the Bell erisophake for the following interlocking reasons:

1. The amount of traction that can be applied with a Bell erisophake cannot be greatly varied without breaking suction and producing annoying slippage of the instrument. If the zonule is resistant, it may be necessary to reapply the erisophake several times before delivery can be accomplished. This limitation on the amount of traction that can be applied and the excessive intraocular manipulation required should slippage occur may adversely affect the eye in the following two ways:

a. Since the balance between traction and counter pressure can only be shifted in the direction of greater counter pressure this should theoretically increase the incidence of vitreous loss in cases with more resistant zonules.

b. The bulk of the erisophake head plus sudden gouging movements against the corneal endothelium incurred during erisophake slippage and reapplication undoubtedly traumatize the endothelium, producing a higher incidence of corneal edema and internal reaction. The latter problem is reduced with forceps for the head of the instrument is smaller and when properly applied has never, in my experience, slipped.

2. The main advantage with forceps, however, is the more flexible range in the relative amounts of traction and counter pressure that can be employed.

A little more traction and a little less pressure can often make the difference between a complicated delivery with massive vitreous loss and a routine extraction. The erisophake operator, with limited traction available, does not have the necessary flexibility to cope with threatened vitreous loss when considerable resistant zonule remains to be lysed before delivery of the lens can be completed.

For these reasons I believe that the capsule forceps remains the instrument of choice whenever a firm grasp of the capsule is possible. I now use the erisophake only when the capsule is too tense to permit forceps application. (These criticisms do not apply to the Barraquer or other motor-driven types of erisophakes.)

Thus from experience gained in over 350 cataract extractions I have concluded that the safest and most effective and psychologically least disturbing way to accomplish lens extraction when the zonule is intact is by the tumbling technique with capsule forceps and I have suggested that this might be referred to as a "closed-eye technique."

When utilizing alpha chymotrypsin, however, these conclusions are no longer valid because the enzyme has altered the anatomic conditions.

Tumbling becomes difficult for two reasons:

1. It is difficult to grasp the inferior pole of the subluxated lens with forceps without a real danger of rupturing the hyaloid face, filling the anterior chamber with vitreous, and possibly pushing the lens deep into the vitreous cavity. For this reason many of those who have worked with alpha chymotrypsin have advocated the erisophake, since it can be applied to the lens surface without putting pressure on the lens.

2. The entire zonule becomes loosened simultaneously through the lytic action of the enzyme, thus there is no zonular attachment at the 12-o'clock position to serve as a hinge or fulcrum. On attempting to lift the inferior pole upward the entire lens tends to ride up and the over-all effect is virtually that of plucking the lens out. This produces undue stretching and trauma to the iris when a round-pupil extraction is being attempted for the lens tries to go through the pupil with its broadest diameter rather than tilting through.

Tumbling with forceps after enzymatic zonulysis is therefore difficult and even somewhat risky. Although the risk can be minimized by employing an erisophake, there is no real indication for its use. With a prelysed zonule, the lens may be delivered by pure traction and, under these circumstances, the sliding technique under direct visualization seems to be the method of choice. Since the lens can be delivered with little or no pressure from below, the risk of vitreous loss (that may occur without the use of enzyme when the lower zonular fibers do not rupture) is virtually eliminated.

In addition the sliding of a free lens from its bed is less disturbing to the hyaloid face than tumbling. The subluxated lens can easily be grasped with capsule forceps tilted sideways near the superior equator while gently supporting the lens from below with the expressor. Grasping the lens at its upper equator under direct visualization reduces the threat of initial rupture of the hyaloid face. If necessary, gentle pressure can be applied over the inferior equator to tilt the upper equator forward slightly to permit forceps application.

After this, delivery is accomplished merely by raising up the superior equator and stripping the iris over the lens. A few rocking movements combined with gentle traction usually suffice to slide the subluxated lens from its bed. The cornea can be made to follow the lens with the expressor but no pressure is needed. If some of the zonular fibers remain attached they usually break without difficulty but, if unusually firm, they may be broken directly with the expressor, as suggested by Kirby.

If the surgeon elects to slide the lens out while using alpha chymotrypsin, rather than to attempt tumbling, forceps regain their effectiveness.

I, personally, prefer them to the erisophake for I believe that they produce less trauma to the endothelium and, at the present time, it is my impression that alpha chymotrypsin may be quite destructive to traumatized endothelium. Even with the utmost care in avoiding endothelial trauma there seems to be a tendency for the eye to react more severely and for the cornea to exhibit mild initial haziness. Whether this is an enzymatic effect or secondary to the increased intraocular manipulation required by the introduction of a cannula behind the four quadrants of the iris, or a combination of these two factors remains to be answered.

Whatever the cause, it would seem worth while to eliminate as much chance of endothelial damage as possible. The sliding technique with forceps appears to be the most effective means of delivery when the zonule is prelysed and also seems to offer minimum danger of additional endothelial trauma.

Summary

Prior to the introduction of alpha chymotrypsin, the tumbling technique with forceps was the most commonly employed and most effective method of lens delivery.

Tumbling is preferred to sliding for in the actual mechanical lysis of the zonule it permits greater amounts of traction and counter pressure to be applied with less danger of vitreous loss. The mechanics of tumbling depend on the presence of an intact zonule.

With the utilization of alpha chymotrypsin the primary indication for tumbling is lost, as the zonule is prelysed and instrumentation is carried out on a subluxated lens. Tumbling under these circumstances is awkward and possibly dangerous.

The anatomically altered conditions call for an almost pure traction delivery with little or no counter pressure. The sliding technique seems to be the method of choice, for it is done under direct visualization and with minimum disturbance to the internal structures of the eye.

Forceps are preferred to the erisophake with and without alpha chymotrypsin, since they permit greater amounts of traction and produce less trauma to the endothelium.

Alpha chymotrypsin should be utilized only in patients with resistant zonules; usually these patients are in the 20 to 60 years age group.

These conclusions are based on a series of 356 cataract extractions.

32 Grove Hill.

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Ophthalmic Miniature

The hard labors of medical life, urged with an imprudent zeal, are too often stopped by death; the man fitted mentally to do most and best, feels keenly the brevity of every earthly career, and strives, by diligence too great for human endurance, to make life most fruitful; but often his harvest is blighted, because the great reaper puts his sickle into the laborer's field.

Henry D. Noyes,
Tr. Am. Ophth. Soc., **2**:64, 1865.

NOTES, CASES, INSTRUMENTS

HEAD PAIN*

Report of an interesting case

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It is well established that, within the symptomatology of the entire field of medicine, headache is probably the most common. It can be due to innumerable causes and frequently presents a problem in diagnosis which is far from simple. The following case is being reported because of the comparative rarity of the final diagnosis and because this rather simple type of presenting symptom was caused by a perplexing and rather baffling lesion.

Case report

P. C., a 16-year-old school boy, who was first seen in December, 1959, complained of a sharp pain localized in the region of the left eye. This pain had been intermittent for two or three weeks prior to the first examination but during the preceding 48 hours had become more severe and the patient had been unable to sleep for two nights. The pain was sharp, lancinating, and was present in the deep left orbital area, coming forward to the eye itself. There was no nausea or vomiting.

Physical examination was entirely normal.

Eye examination revealed a slight narrowing of the left palpebral fissure but otherwise was entirely negative. Visual acuity and ocular motility were entirely normal and there was no error of refraction. There was no evidence in the ocular fundi of increased intracranial pressure and the fields of vision were normal. Nevertheless, the pain persisted in an intermittent fashion. During the following 48 hours, while he was playing hockey, the pain became extremely severe and persisted through the night. It was rather constant at this time. The patient was again seen by his local physician and, because of the persistent pain, he was admitted to St. Elizabeth's Hospital, Brighton, Massachusetts, for further study.

While in the hospital physical examination was not remarkable. Laboratory data showed normal spinal fluid—clear fluid with no cells and normal chemistry. Blood examination and urinalysis were normal. There was no evidence of any organism in the spinal fluid after a period of 72 hours.

During his stay in the hospital there was never any temperature reaction. X-ray films of the sinuses and chest were negative. An electro-encephalogram was normal. The patient was seen by a neurologic consultant, who believed that the headache might be due to an intracranial aneurysm. A left carotid arteriogram was done, which showed a large cerebral aneurysm arising from the posterior cerebral branch of the left internal carotid artery. Examination of the carotid on the right side was normal.

A few days later the patient was operated upon by a neurosurgeon. A clamp was placed upon the left common carotid artery, which was gradually tightened over a period of four days, when the artery was permanently ligated. The patient was discharged from the hospital shortly afterward and has had no symptoms since.

Comment

This case demonstrates the rather exceptional occurrence of an intracranial aneurysm causing severe headache in a 16-year-old youth. It emphasizes the necessity of thorough and painstaking investigation of all cases of persistent headache.

In most cases, an intracranial aneurysm is silent and, not until bleeding occurs, is its presence evident. Occasionally, however, as a result of compression of cranial nerves, there may be signs and symptoms. Intermittent or chronic headache of the migraine type may occur. Ocular muscle paralysis of partial or complete degree may involve muscles supplied by the third or sixth cranial nerve. Homonymous of bitemporal field defects or amblyopia may occur, depending on whether the optic nerve, the chiasm, or the optic tracts were compressed by the aneurysm. These signs are applicable to unruptured lesions, while the sudden onset of head pain followed by mental confusion, intraocular hemorrhages, coma, or even hemiplegia point to leakage or rupture of the aneurysm. The headache is present in all cases and is of severe degree. It may be localized to the occiput or to one side of the head at first but later becomes generalized.

Incidence

Until recent years, intracranial aneurysms have largely been discovered at necropsy so that it is difficult to ascertain their true in-

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cidence. Turnbull,[1] in 1918, reporting from the pathology division of the London Hospital, stated that in 4,547 examinations of the head in 6,751 autopsies during the period 1908 to 1913, 1.36 percent showed aortic aneurysms; aneurysms of the cerebral arteries occurred in 0.92 percent of examinations.

Cushing,[2] in a report of 826 verified and 454 unverified intracranial neoplasms, in 1923, found only four proved cases of aneurysms of the internal carotid artery; two other unsuspected ruptured aneurysms were discovered at autopsy. Sosman and Vogt[3] found four aneurysms in 284 brain autopsies and four cases in 297 autopsies from the medical clinic of their hospital.

Richardson and Hyland,[4] of Toronto, discovered 40 cases (0.87 percent) of intracranial aneurysms in 4,618 necropsies. Courville[5] found 96 intracranial aneurysms in a series of 30,000 autopsies, about 0.58 percent of the total. However, Poppen[6] pointed out quite strikingly that if a vigorous effort is made to search for aneurysms, more would be discovered, as shown by his report. There were only nine cases encountered in a series of 110 surgical patients with intracranial aneurysms over a 10-year period, while during the next four years 101 cases were found, chiefly due to a more concerted diagnostic effort.

It is, therefore, difficult to state the incidence of these cases in the population at large but a reasonable estimate would be about 0.5 to 1.0 percent.

Age and sex

Dandy[7] stated that below the age of 20 years few cases are found, and thereafter the occurrence is about equal during the various decades until the age of 70 years, at which time they decline. This observation would seem to hold true in most of the reported series. Various authors have reported isolated cases in the very young and the very old. It would appear from an analysis of several series of cases reported by various authors that intracranial aneurysms are likely to occur in approximately an equal distribution in both sexes; some authors reveal a slight preponderance in men, while others report the same for women.

Etiology

There are several types of intracranial aneurysms, the etiology of which may be fairly obvious or very obscure and which present one of the most interesting aspects of the problem. The reported causes are heavily biased by the opinions of individual authors, and there seems to be no general agreement as to the preponderance of any one etiology. The various causes are mycotic, traumatic, luetic, arteriosclerotic and the so-called "berry" or congenital types. Mycotic aneurysms are caused by emboli containing pathogenic organisms lodging in the small arterioles or in the vasa vasorum of larger arteries; this usually takes place during the course of a septicemia or bacterial endocarditis. Hemorrhage, often along the course of the middle cerebral artery, occurs and these lesions are often multiple and may produce pyogenic lesions of the brain.

Trauma has been reported as a cause of aneurysm, but most of these cases seem somewhat questionable. An aneurysm of an intracranial vessel produced by trauma must be considered very exceptional. Arteriovenous aneurysms are a different matter. Aneurysms due to lues must also be considered; recent authors have disputed earlier beliefs that luetic disease causes many of the cerebral vessel aneurysms. This disease probably causes a good percentage of aneurysms elsewhere in the body but few in the brain blood vessels.

In the cases reported as due to arteriosclerosis there seems to be some doubt as to the correctness of the interpretation of the pathologic lesion by different observers. Tuthill[12] concluded that the "reported incidence of arteriosclerosis as a cause of aneurysms by various writers has no common basis, hence cannot be authoritative." If arteriosclerosis

were the chief cause of intracranial aneurysms, the majority of the lesions should be located on the basilar-vertebral portion of the circle of Willis, since these vessels are the most extensively involved by arteriosclerotic changes. However, the contrary is true, and therefore it is likely that some other factor is responsible.

It is on the etiology of the congenital or berry aneurysms that the most fascinating work on the problem has been done. Much research into the defects of the blood vessel wall has been done; upon the mechanism of their occurrence from the development of the primitive vascular network embryologically, and whether the defect may occur in the media, intima, or elastic membrane.

In summary, one reaches the conclusion that the origin of the small "berry" aneurysm from which develop the majority of subarachnoid hemorrhages is not conclusively known. They may result from congenital medial defects as the result of overstretching and rupture of the elastic membrane—possibly arteriosclerosis enters into the picture—or they may develop from persistent remains of the embryonic capillary network.

As Carmichael[13] has said:

"If the mere existence of a minute developmental gap in the muscular coat of an artery were enough to determine the formation of an aneurysm, almost every circle of Willis would bear a generous crop of tiny aneurysmal sacs and most of us would die from meningeal hemorrhage in childhood or early youth."

Medial defects in the artery wall are extremely common and congenital aneurysms are relatively rare, presumably because the internal elastic membrane offers a barrier to expansion induced by the pressure of the circulating blood flow. We still have no definitive answer to this interesting puzzle.

Diagnosis

Like other cerebral lesions, such as neoplasms, the diagnosis of an intracranial aneurysm depends upon it location and possible compression of surrounding structures. Many small aneurysms, which cause no pressure symptoms, may go undiagnosed until necropsy; while others, undergoing sudden rupture, may produce subarachnoid hemorrhage; still others, gradually increasing in size, may cause symptoms through compression of various cranial nerves and thus suggest their location, but still remain indistinguishable from neoplasms in the same area.

Ocular muscle paralysis is frequently caused by pressure or rupture of intracranial aneurysms, the most frequent nerve involved being the oculomotor. Usually pain in the eye is present and, in more pronounced cases, ptosis, pupillary dilatation and fixation, and paralytic exotropia develop. In several instances, return of ocular muscle function takes place following regeneration of the nerve. Exophthalmos has been commonly caused by large expanding aneurysms occurring in the cavernous sinus and obstructing venous drainage from the orbit.

Various visual field defects may be produced by intracranial aneurysms as pressure is exerted upon the chiasm, optic tracts and radiations, or upon the optic nerve itself; obviously, these various effects would depend upon the location of the lesion.

Pain of trigeminal origin is commonly experienced with basal aneurysms, often associated with cranial nerve palsies; in several instances the pain may be typical of trigeminal neuralgia. Dandy[8] has reported eight of 21 patients with aneurysms of the vertebral and basilar arteries having tic douloureux.

In a further effort to establish diagnosis, X-ray films may be of aid. In 1926, Sosman and Vogt[3] emphasized the outstanding features of X-ray findings: calcification in the aneurysmal wall and erosion of the bone adjacent to the aneurysm and enlargement of the sella turcica, the optic foramen and superior orbital fissure. Erosion of the margin of the carotid canal and displacement of the pineal body are helpful findings which point to the localization of the lesion.

Cerebral angiography

Following its introduction by Egas Moniz[9] of Lisbon, in 1927, cerebral angiography has become an important procedure in making the diagnosis of vascular brain lesions. He employed this method in the diagnosis not only of vascular but also of neoplastic diseases of the brain.

Angiography basically is the injection of a radiopaque substance into a carotid artery and making X-ray films while the circulating material fills the vessels. This involves making the roentgrams rapidly enough so that the large vessels, the small arteries and veins may be visualized before the material passes through the vessels, usually a period of about four seconds. Obviously, this requires special techniques and special equipment. Today, many neurosurgeons believe angiography is mandatory when a vascular lesion of the brain is suspected. Other older surgeons, notably Dandy[10] never recognized it as worthwhile, believing that in most instances the clinical signs and symptoms would point to the diagnosis. However, since such cases were largely those of the infraclinoid and supraclinoid portions of the internal carotid artery, general feeling among neurosurgeons at present is that cerebral angiography is a valuable and important aid in diagnosis, and it is quite universally employed. Multiple aneurysms occur in from five to 30 percent of cases and, when a single aneurysm has been demonstrated, complete bilateral angiograms are of great importance.

Treatment

The problem of treatment of intracranial aneurysms is one of proper surgical approach. There have been two methods applied: (1) an attempt to diminish the blood flow through the involved portion of the circle of Willis by occluding the ipsilateral internal or common carotid artery extracranially; (2) a direct attack upon the aneurysm itself.

Results of carotid ligation reported by various surgeons reveal that prevention of bleeding from aneurysms of the circle of Willis may be accomplished by this procedure. The experience on which carotid ligation is based is that ligation will so reduce the pressure and pulsation within the aneurysm that the walls will thicken, the aneurysm will become smaller and there will be less danger of rupture. In many instances, however, complications of hemiplegia, hemiparesis, and further hemorrhage ensued. The local lesion obviously remains and its future behavior is not predictable.

A better possibility of cure is offered by direct attack upon the lesion. This technique, although hazardous, involves "trapping" the aneurysm between clips or surrounding the lesion with muscle tissue. The results are largely disappointing, for many of these aneurysms occur in the area of the main blood supply to the motor and speech areas of the brain and unfortunate complications often ensue. Surgical results will probably remain poor.

Of paramount importance is preoperative knowledge of the relation of the lesion to normal blood vessels. This requires good angiograms made in anteroposterior and lateral exposures and the point of the lesion's communication with the arterial tree. If one knows beforehand that the lesion is ruptured, treatment will then require obliteration of the vascular supply from the opposite as well as the involved side. It appears that the greatest hazard is the rupture of the aneurysm during its exposure, which often leads to the occlusion of vessels not properly recognized. In 1944, Dandy[7] stated that if both anterior cerebral arteries were sacrificed, life was lost; Poppen,[11] however, reporting 10 patients who had ligation of one or both anterior cerebral arteries, stated that, by keeping the blood pressure normal during the procedure, the patient did not remain in coma or die.

A review of results of treatment of various authors is depressing and would point to the seriousness of intracranial aneurysms. The mortality rate was almost 50 percent. With recent improvements in angiography, however, the rate is being reduced, and more re-

cent results remove to some degree the attitude of pessimism.

Summary

A case of severe head pain localized around the left eye which proved to be due to an intracranial aneurysm of the left posterior cerebral artery has been presented. Certain features related to such lesions were discussed.

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AN UNUSUAL CASE OF HEMIANOPIA*

From cerebral anoxia at high altitudes

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Man's ability, or lack of it, to adapt to high altitudes has been studied for some time from two main points of view: (1) the chronic effect of high altitude, such as observed in settlements in the Peruvian Andes, and the resulting chronic mountain sickness (Monge's disease) in susceptible individuals[1-3] and (2) the acute effects, such as those seen during the expeditions that climbed Mt. Everest.[4,5]

A recent Austrian study on acclimatization to a height of 6,000 to 9,000 feet revealed the interesting and hitherto unsuspected fact that adaptation to this altitude appears to go through several phases.[6] On measuring the exercise tolerance of university students in the Alps, Halhuber, et al., found not only the expected increased lability of vital signs during the first day in the mountains but also a second period of reduced tolerance in the third week. It is therefore suggested that in cases of accident or illness occurring during mountaineering or skiing expeditions, the length of time the patient had been in the mountains should be recorded carefully.

Case report

The patient, a 31-year-old submarine officer in the Chilean Navy, had been in good health until August 24, 1957. He had been undergoing vigorous training for three weeks at an altitude of 6,000 feet, preparatory to an antarctic assignment. On the day of onset of the present illness he took part in a march, on skis, to a height of 9,000 feet. Several members of the group had to drop out of the exercise throughout the morning and return to camp. As the remainder were nearing their goal, the patient felt increasingly fatigued but kept on going because he felt he should set an example, as he was the senior Naval officer present. Just before

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reaching the top of the mountain he suffered a sudden onset of blurring of vision in both eyes. He nevertheless proceeded the rest of the way. After lying down and resting for about 20 minutes at the summit, he had recovered his vision and his strength and was able to start the descent. However, the symptoms recurred in a short while. This time they did not clear up, and he eventually had to be taken back to camp on a sled. At that point his vision cleared except for inability to see anything in his right visual fields. He also noted a feeling of coldness in the middle three fingers of his left hand, associated with pallor of these fingers. Forty-eight hours after the onset of his illness he was admitted to the Chilean Army Hospital in Santiago, Chile, where all examinations proved normal except for the presence of a right homonymous hemianopsia. Treatment with vasodilator drugs was unsuccessful.

The patient was then transferred to the Chilean Naval Hospital in Valparaiso. Here he was again found to have a right homonymous hemianopia and also slight weakness with hyper-reflexia on the left. An EEG showed generalized slowness and depression of cortical activity with normal response to photic stimulation. By this time the pallor and cold feeling in the fingers of his left hand had cleared up but recurred temporarily every time he took a cold shower. Eventually this symptom disappeared altogether. A diagnosis was made of infarct of the left calcarine cortex due to anoxia produced by the unusual exercise and altitude.

He was next seen at the U. S. Naval Hospital, St. Albans, New York, on April 9, 1958, at the request of his commanding officer for another evaluation. Complete neurologic examination at this time was entirely negative, except for a right homonymous hemianopia. X-ray films of the skull and chest and a spinal tap were all normal. An EEG revealed a very low voltage tracing throughout. Ophthalmologic consultation revealed a congruous right homonymous hemianopia with macular sparing. Visual acuity was 20/30, bilaterally, correctible to 20/20.

Discussion

It would appear that the patient suffered an infarct of the left calcarine cortex due to the lower oxygen tension and the severe exertion. In view of the mode of onset of the symptoms and the subsequent stationary course of the illness, further studies, such as an arteriogram or an air study, were not considered to be indicated.

We were struck by the fact that this accident occurred at the altitude and the time highlighted by the study from Innsbruck already quoted. Thus, this critical period in altitude adaptation has clinical and pathologic implications, as well as being an intriguing and, as yet, unexplained physiologic discovery.

Why the third week should be such a vulnerable period—if future work shows that it indeed is—remains a tantalizing question. It is tempting to try to explain this situation in terms of the concepts postulated by Laborit regarding the individual's reaction to stress.[7,8] According to this theory, stress elicits a sympathetic reaction which in turn stimulates the parasympathetic system. This may overshoot the mark, if the original displacement is of sufficient magnitude, and, if so, again provokes a sympathetic discharge as the body tries to re-establish homeostasis. It appears conceivable that at this point the individual would be rather vulnerable to any additional strain. Under such circumstances, the increased oxygen demand provoked by heavy exercise in the face of reduced oxygen supply due to the altitude could very well have outstripped the patient's ability to maintain homeostasis and resulted in the infarct he suffered.

An alternative possibility would be that the patient had pre-existing disease of the calcarine branch of the left posterior cerebral artery, such as an arteriovenous malformation. The strenuous circumstances to which he was exposed might then well have caused a hemorrhage or a thrombosis in this already vulnerable region. While the sequence of events at the onset of the illness and the patient's subsequent course do not suggest this as the most likely explanation, this diagnosis was, of course, not completely ruled out.

Although no definite conclusions can be drawn from this experience, it does emphasize the need for more precise information regarding the effects of high altitude and how adaptation to it may be achieved.

Summary

A case of cerebral ischemia which occurred in a previously healthy adult male at an altitude of 9,000 feet is reported. The literature is reviewed and the possible pathologic mechanisms are discussed, as well as the implica-

tions regarding man's adaptation to high altitude.

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ACKNOWLEDGMENT

I wish to express my appreciation to Dr. A. Varas-Espejo, Lt.Cdr./Chilean Navy, who brought this case to my attention and kindly made the records of the examinations in Chile available.

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AN EYE SPECULUM FOR ANIMAL SURGERY*

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Exposure in animal surgery is sometimes difficult because of trouble handling the lids and nictitating membrane. Human speculums are generally unsatisfactory, being difficult to maintain in position and usually resulting in poor exposure. Lid sutures may be used but are inconvenient and often give inadequate exposure.

A simple, sturdy, self-retaining speculum was devised. It consists of a length of spring steel wire, fashioned with several small hooks to retract the lids, and is gently curved to conform to the palpebral fissure (figs. 1 and 2). It will stay from its own tension or may be locked in place. The nictitating membrane may be pulled aside with the hook on the speculum.

The speculum, which may be obtained from the authors, affords excellent exposure, eliminates lid pressure, and gives an uncluttered field.

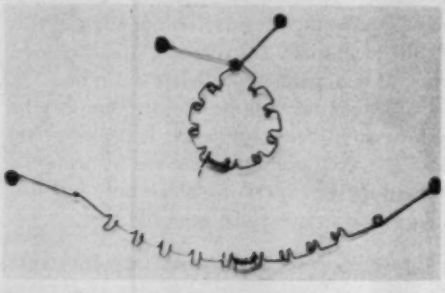

Fig. 1 (Thomas and Terry). An eye speculum for animal surgery.

Fig. 2 (Thomas and Terry). The eye speculum in place.

* From the Department of Ophthalmology, Bowman Gray School of Medicine. This work was supported by USPH grant B-1243, and the Marguerite Barr Moon Foundation.

SOCIETY PROCEEDINGS

Edited by DONALD J. LYLE, M.D.

YALE POSTGRADUATE SERIES

November 20, 1959

MODERN THERAPY OF UVEITIS

DR. DAN M. GORDON (New York): Corticosteroid therapy is indicated in the management of uveitis, in the absence of more specific therapy. Its use early enough, frequently enough, and long enough will often prevent considerable ocular damage, or even blindness. The present method of routine survey for etiology has proved unsuccessful because we lack the ability to pinpoint the cause of most cases of uveitis. In addition, we possess very little in the way of specific therapy. Too often, the uveitis survey is substituted for therapy and the eye is permitted to become damaged while treatment is delayed or permanently withheld. "Positive" findings on survey do not necessarily mean that one has discovered the cause of the uveitis.

Knowledge of how to handle corticosteroid therapy is necessary for success in the management of intraocular inflammations today. Corticosteroid therapy is not a new series of drugs but rather is a new concept. For that reason, one must devote time to acquiring skill in application if one wishes to give patients the benefit of modern therapy. An understanding of the pathology of granulomatous uveitis makes obvious the rationale for combined corticosteroid-antimicrobial therapy, and may explain some reported failures.

It must be understood that corticosteroid therapy employing either the topical preparations or the oral-intramuscular natural and synthetic steroids or corticotropin (ACTH) is symptomatic therapy. The indications are inflammation, edema, allergy, granulation tissue, and certain infections (here concomitant antimicrobials are mandatory). The contraindications are keratitis due to herpes simplex, chickenpox, smallpox, and fungi, as well as the usual systemic contraindications.

Discussion. DR. PHILIP BONDY of the Department of Internal Medicine opened the discussion saying that "he had come to scorn but remained to praise."

When steroids are given in lupus erythematosis, Dr. Bondy warned against the sudden cessation of the drug due to systemic adrenal hypoactivity. Local eye steriods are preferable when possible. If one could avoid using steroids systemically many serious problems could be avoided. Dr. Bondy pointed out that osteoporesis is not usually demonstrable even by X-ray films until much of the bone is gone. With careful control of systemic dosage one can reduce this somewhat but not entirely.

With ACTH, which is effective in ulcerative colitis, internists find themselves using very large doses, although Dr. Bondy feels that 25 units in 18 hours is larger than the amount necessary to produce a response.

Dr. Bondy believes that double-blind tests on these products should be done to get a better evaluation of their effects. The doctor giving the medication and the patient taking the medicine should not know what product is being used. Some such testing has been done in arthritic and ulcerative colitis cases. It would be useful to repeat these studies in eye cases in order to obtain an unbiased opinion of the steroids, their effects and side-reactions.

DR. GORDON replied that while a number of patients do well on one product, they respond poorly when another is used. The maximum endocrine effect of a steroid, for instance at 100 mg., may not give maximum anti-inflammatory effect. In ophthalmology, one is treating rather healthy patients, as compared to arthritics who have sick tissues all

over the body. Dr. Gordon has returned to subconjunctival injections in some cases. In general, his failures are in those cases with whole quadrants of choroidal abscesses and in those cases that suffer rebound due to sudden cessation of the drug.

Dr. Louis Raymond stated that he felt many uveitis cases have definite etiologic factors and pointed out Staph-toxoid sensitivity in three specific cases. Two of the cases were first treated with ACTH and had a remission with considerable orbital edema. Then on small doses of Staph-toxoid injections, both improved without any recurrence. The third case, one with episcleritis treated with steroids, showed sensitivity to tree pollens and seemed to respond to desensitization.

Dr. Gordon expressed concern as to the effects of skin testing and wondered whether this might not set up conditions for an allergic reaction at a later date. He believes that uveitis is a hypersensitivity.

Stephen Troubalos,
Recording Secretary.

CHICAGO OPHTHALMOLOGICAL SOCIETY

October 5, 1959

Clifford P. Sullivan, M.D., *presiding*

Bilateral uveitis with Entamoeba histolytica

Dr. Dennis Harris, London, and Dr. Carroll Birch reported the findings in an 18-year-old white youth with bilateral diffuse chorioretinitis with marked pigmentary disturbances. Trophozoites of Entamoeba histolytica were found in the patient's stools. The remainder of the etiologic survey was negative. The patient was treated with amebacidal therapy and local cycloplegics and the uveitis subsided with considerable improvement in visual acuity. Dr. Birch, in discussing the paper, stated that patients who had been given purges yielded a higher percentage of stools positive for parasites. Also, the Puerto Rican and Mexican patients in their study showed a higher percentage of parasites in the gastrointestinal tract than other national groups. She stated that an attempt is now being made to study the stools of patients of approximately the same age and nationality as those in the uveitis group.

Discussion. Dr. Peter C. Kronfeld: I wish I could say something here that would lend support or strength to the rather tenuous evidence for an amoebic etiology of the case presented here. Unfortunately, I cannot. I spent six years in North China and in that particular part of the world, amoebiasis, at that time, was endemic—among the Chinese as well as among the white population. The relationship between parasite and host varied within wide limits—meaning that some of the people we saw were very sick and others were what we called carriers. Still, I saw a good many amoebic abscesses of the liver and I was present at several autopsies of patients who had died of amoebic brain abscesses. In these many cases of carriers and sick people, I don't remember having seen any ocular involvement.

However, the unusual clinical picture in this case deserves special consideration. Although we didn't see the early stages of the disease, we know it was a panuveitis, chiefly infiltrative with very little exudate and with profound visual disturbance. This permits us to think of an unusual etiology.

I would like to ask Dr. Birch two questions. Does she think that the complement fixation test studies of the blood and aqueous performed quantitatively and serially several times during the patient's illness might have provided at least tentative evidence in favor of an amoebic etiology? And, secondly, what does the modern parasitologist think of the possibility of a second invader, bacterial or viral, establishing itself in a patient with amoebiasis? Is it possible that only because of such a combination of infectious agents does the patient show the ocular picture described?

DR. BIRCH: The complement fixation test in amoebiasis in Craig's hands was 87-percent reliable. Unfortunately, in other hands, it did not prove to be quite so reliable. The preparation of the antigen for this test is difficult. I don't know of any place in this country where the test is now being done. We do know, of course, that such other parasites as loa loa, blinding filaria, cysticercus, and taenia have a predilection for the eye tissues.

DR. HARRIS: As Dr. Kronfeld pointed out, the only evidence of an etiologic connection was the ocular improvement coincident with the administration of amebacides. We considered the possibility of performing blood complement fixation studies but we were unable to find a laboratory in the United States where the test was still being performed.

PRESENT STATUS OF THE ANTERIOR CHAMBER LENS

DR. DUPONT GUERRY, III, M.D.: See Am. J. Ophth., **50**:250-258 (Aug.) 1960. Questions from floor follow.

Discussion. DR. DAVID SHOCH: A New York cardiologist named Oppenheimer, some five years ago, was wrapping kidneys in plastic material—polyvinyl, and so forth. He found accidentally that this resulted in tumor formation around the kidneys of rats and other experimental animals. This has been amply duplicated, and now the implantation of plastic materials within tissues is a standard technique for the investigation of experimental tumors. All people who are interested in the study of cancer use this as an experimental tool.

I'm not at all sure that Dr. Guerry was speaking about the same type of plastic but the question does arise—Are these plastics that are being inserted into the eye capable of stimulating tumors within the eye? All these have been experimental techniques, and I wondered whether some of the tissue effects that Dr. Guerry and perhaps others have noted with these plastic inserts, might be a variety of stimulation of tumor growth found elsewhere with implantation of plastic materials.

DR. GUERRY: We are all aware of the fact that certain of acrylic materials can give rise to tumor formations. In our particular work we have not encountered the reaction, nor have any of the European workers described it. Schreck mentions the fact that he will not put an anterior chamber lens in a case where there is any fibrosis going on in the anterior segment, because of its tendency to stimulate fibrous tissue proliferation. There has been no evidence of induced neoplastic growth in any of the cases investigated.

DR. HOWARD WILDER: How easy is it to see the peripheral retina in an eye with such an implant?

DR. GUERRY: Unless the pupil can be widely dilated, one does not get a good view of the retinal periphery. If the pupil can be dilated beyond the size of the lenticulus the periphery of the retina is seen as in an aphake. We have a patient with a retinal detachment who had an anterior chamber lens insert done elsewhere. Fortunately, the retinal tear was in an area far enough back so that it could be visualized easily.

DR. DANIEL SNYDACKER: I wonder if Dr. Guerry would say a word about extracting these lenses in cases where complications may arise?

DR. GUERRY: I have had no experience. The two Schreck lenses that we put in for some friends further south were taken out by them. I understand that it wasn't too difficult. They had had occasion to remove Ridley lenses in the past, and stated that the anterior chamber lens afforded less trouble. The Europeans report that they simply make a keratome incision, break up any synechias, and lift out the implant with an iris hook. I hope it is not going to be a pressing problem.

DR. THEODORE SHAPIRA: How would Dr. Guerry explain the need for orthoptics? Is there, perhaps, some muscular imbalance or prismatic effect induced after the insertion of one of these lenses?

DR. GUERRY: The two cases in which or-

thoptics was necessary had had their cataracts for about five years. Both had a pronounced muscle imbalance and both patients needed muscle surgery and orthoptics to bring them around. They now have fusion.

Factors influencing depth of anterior chamber

Dr. Daniel Snydacker, in discussing the anatomic and physiologic factors which influence the depth of the anterior chamber, pointed out that shallowness of the anterior chamber in otherwise normal eyes is a phenomenon of senility. He described experiments in which he measured the depth of the anterior chamber in patients who were to have cataract extractions and then measured the volume of the lens after its removal. Generally he found that there was a correlation between the chamber depth and lens volume: the shallower the chamber, the larger the lens. He found certain important exceptions, however, which led him to believe that other factors than lens volume might be operative in some cases. Attempts to implicate the vitreous were negative; injecting saline into the vitreous of rabbit eyes, thereby increasing its volume, produced no change in depth of the anterior chamber.

By exclusion, he therefore concluded that the ciliary body was responsible for decreased depth of the anterior chamber in at least some cases. He recounted the difficulties of proving this theory and said that the science of cryogenics might provide the answer to the problem.

Discussion. Dr. Maurice Kadin: You can immerse the head of the rabbit in a box and pour liquid nitrogen over it and immediately fix the eye with all its fluid.

Dr. Snydacker: I investigated the possibility of quick freezing and I am sure maybe new techniques have been evolved since I investigated. My impression at the time was that the freezing was not so quick that the fluid balance in the tissues was unaltered.

Manuel L. Stillerman,
Corresponding Secretary.

Ophthalmic Miniature

Thomas Sharp (Hos. Reg. No. 5276) aged twenty-eight, eleven months ago of H.M.S. Wasp, able seaman, at Lisbon, had an eruption and other secondary symptoms; was sent ashore to the British Hospital, and took iodide of potassium and sarsaparilla; he soon got better, but had pain in the eyes, very severe inflammation supervened, and for six weeks he was "blind," took "mercury pills" and when decidedly salivated, he got better again, although still nearly blind; had three "relapses" and was invalided to England.

Ophthalmic Hospital Reports, 1:6, 1857.

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GLAUCOMA*

The various ocular disorders which are grouped together as glaucoma are marked by ischemia of the distal visual nerve elements—those either of the retina itself or of the optic nerve. This has long been held to be the end-result of a disturbance of the ocular circulation provoked by causes some of which are apparent (as in many cases of secondary glaucoma) but which mostly are unknown.

In a high proportion of cases of primary glaucoma the cause is thought to be mechanical compression of the nervous tissues or their nutrient vessels—a mechanism which is perhaps most clearly evident in the congestive form of glaucoma where venous congestion

* Reprinted from *The Lancet,* July 9, 1960, p. 83.

and edema of the ocular tissues are associated with a clear increase of intraocular pressure. On the other hand, in the insidious form of primary glaucoma (simple glaucoma) selective atrophy of bundles and sectors of optic-nerve fibers often proceeds silently without the tension increasing much. Nevertheless, in view of the considerable rise of tension in the advanced stage, pressure is generally believed to be at least the proximate cause of glaucomatous atrophy; and, because at earlier stages tonometry so often shows the pressure to be within normal limits, the accuracy of tonometric methods has been questioned. This has led to the development of more refined methods of tonometry—in particular, the applanation tonometer of Goldmann.[1]

Another view is that glaucoma may result from disease of the nutrient vessels which renders them vulnerable to normal pressures; and indeed in the unusual "low-tension glaucoma" typical glaucomatous atrophy is found without raised ocular tension. This type has been ascribed to the vascular sclerosis and cavernous atrophy in the optic nerve that was originally described by Schnabel;[2] and it now seems probable that similar changes underlie other forms of primary glaucoma. In 1945, Loewenstein and Garrow[3] described a form of spongy degeneration of the optic nerve which they believed preceded the cavernous atrophy; and two years later Wolff[4] suggested that sclerosis played an important part in the production of optic-nerve ischemia in primary glaucoma of various types. Cristini,[5] employing Pickworth's staining method to examine eyes enucleated in an advanced state of glaucoma, detected diminution in the number of vessels in the capillary network of the papilla and retrolaminar part of the nerve, and concluded that this was the essential pathologic change in cavernous atrophy and accounted for the manifestations of glaucoma throughout the eye.

Duke-Elder[6] regards the mechanical obstruction of the angle of the anterior chamber —generally believed to be the cause of the raised tension in simple glaucoma—as itself a product of vasosclerosis, probably affecting tissues in the region of the trabeculae and canal of Schlemm and thus obstructing the aqueous outflow. Such sclerosis may result directly in ischemic optic atrophy if it affects chiefly the posterior segment of the eye; or, if the outflow channels are most affected, in hypertension. Thus raised tension, which is irregularly associated with early glaucomatous atrophy, may be but one result of a process which, even without rise of tension, may produce ischemia; and this ischemia is further aggravated by the effects of mechanical compression when the intraocular pressure rises.

The first result of obstruction of the aqueous exits is accentuation of the normal diurnal pressure variations rather than an absolute rise of tension; and experimental work indicates that this may represent an aberration of a normal homostatic mechanism. The linear rise in tension observed when an excised eye is perfused with fluid is matched in the living eye by an initial rise followed by a period in which the tension remains static before finally increasing again, as though the intraocular pressure were controlled by a mechanism effective within certain limits but overcome by increasing stress. When the sympathetic nerve supply to the eye is interrupted the pressure rise resembles that in the excised eye. That this nervous control may be mediated through a hypothalamic center is suggested by the work of von Sallmann and Lowenstein[7] and of Gloster and Greaves.[8] Afferent impulses to this center are believed to arise in the region of the trabeculae, and further work is being undertaken to determine the pathway of vasodilator efferents antagonistic to those of the sympathetic.

In diagnosis measurement of the intraocular pressure, however accurate, is less important than observation of its fluctuations, or provocative tests which, by increasing the pressure on the aqueous exit channels or obstructing them further, demonstrate their

relative incompetence. All such tests are based on assumptions—for example, the constancy of scleral rigidity, of episcleral venous pressure, and of aqueous formation during tonometry—whose validity is not established. Duke-Elder, while admitting that the water-drinking test has a limited value in indicating the competence of the outflow channels, prefers Blaxter's[9] bulbar compression test to Grant's[10] tonography for determining organic obstruction at the chamber angle. Assessments of the optic-nerve damage by careful ophthalmoscopy, perimetry, and campimetry remain sheet-anchors in the early diagnosis of simple glaucoma; and unless impaired function is detected by such examinations Duke-Elder recommends the withholding of surgical treatment. Miotics (pilocarpine, eserine, and, in emergency, diisopropylfluorophosphate) remain of value in medical treatment—supplemented in some cases by the carbonic-anhydrase inhibitors, acetazolamide and methazolamide. General measures to improve the systemic circulation are also useful.

1. Goldman, H.: Applanation tonometry. In Glaucoma: Transactions of the Second Conference, Dec. 3-5, 1956 (edited by F. W. Newell). New York, 1957, p. 167.
2. Arch. Augenh., **24**:273, 1892.
3. Loewenstein, A., and Garrow, A.: Am. J. Ophth., **28**:240, 1945.
4. Wolff, E.: Tr. Ophth. Soc. U. Kingdom, **67**:133, 1947.
5. Cristini, G.: Brit. J. Ophth., **35**:11, 1951.
6. Duke-Elder, S.: Canad. M. A. J., **82**:293, 1960.
7. von Sallmann, L., and Lowenstein, O.: Am. J. Ophth., **39**:11, 1955.
8. Gloster, J., and Greaves, D. P.: Brit. J. Ophth., **41**:513, 1957.
9. Blaxter, P. L.: Brit. J. Ophth., **37**:641, 1953.
10. Grant, W. M.: Arch. Ophth., **44**:204, 1950.

OBITUARY

PERCY H. FRIDENBERG (1868-1960).

On June 2, 1960, Percy H. Fridenberg, one of the leading ophthalmologists in the United States, died at Nyack, New York. He had practiced and contributed to the advancement of ophthalmology for 69 years. He received his B.A. degree from Columbia University in 1886 and, two years after graduation, while a student of medicine, he wrote the Alma Mater official song, *Sans Souci*.

He was graduated in medicine in 1891 from the then German Kaiser Wilhelm University at Strassbourg. Under the influence of a professor of ophthalmology, Laqueur, he early developed an interest in the eye, and his inaugural dissertation was on the subject, "Ueber die Stern Figur der Krystall Linse." After settling in New York, he interned at Mt. Sinai Hospital, and at the time of his death was the oldest alumnus of Mount Sinai Hospital. He joined the staff of the New York Eye and Ear Infirmary, and most of his early contributions to ophthalmology appeared in the New York Eye and Ear Reports. Later his papers appeared in the *Archiv fuer Augenheilkunde*, *Transactions* of the American Ophthalmological Society, *Journal* of the American Medical Association, *Archives of Ophthalmology*, *Transactions* of the American Academy of Ophthalmology and Otolaryngology, *Transactions* of the American Otological Society, *New York Medical Journal* and *Long Island Medical Journal*. (In his early years he was a triologist, that is, an eye, ear, nose and throat practitioner and a member of the American Otological Society.) In the 1920s he became interested in endocrinology in relation to the eye, and contributed the chapter on "Disorders of metabolism and internal secretions in relation to the eye" to Lewellys Barker's *System*. In the 30s his interest centered on injuries of the eye.

He was professor of traumatic ophthalmology at the New York Post-Graduate Medical School and Hospital and illustrated his lectures with his own drawings of fundi. He was a water-colorist and was an active member of the New York Physicians Art Club. Another one of his hobbies was the history of the City of New York and he

lectured on the subject frequently at educational institutions and clubs. Later he developed an interest in philology to which he brought not only a mastery of English literature but of French and German as well. Some of his papers were written in German. This led him to a study of the history of human speech and he worked on a book under the intriguing title, *From Hand to Mouth*. His preparation for this task was a life-long interest in neurology, psychology, and philosophy, as is evidenced by a paper written by him about 1905 on "Teleology and interpretation of nystagmus and vertigo." He was certificated by the American Board of Ophthalmology in 1919. He was a vice president of the American Academy of Ophthalmology and Otolaryngology and a member of the American Ophthalmological Society. He was also one of the founders and a past president of the New York Society for Clinical Ophthalmology. He had built up a fine ophthalmic library which he distributed in his later years to libraries and friends.

A brilliant conversationalist and a gifted orator and scholar, Dr. Fridenberg was a gentleman of the old school, a cavalier "sans peur et san reproche."

Senator Ernest Gruening of Alaska, son of another ophthalmologist, Emil Gruening of New York City (long deceased) is a nephew of Dr. Fridenberg, whose sister Mrs. Ruth F. Goodman of San Francisco survives him.

Morris Davidson.

CORRESPONDENCE

Fluorescein in Applanation Tonometry

Editor,
American Journal of Ophthalmology:

In a recent article in The Journal,* Dr. Moses has drawn attention to the errors in the estimate of the applanation area of the Goldmann tonometer which result from the low visibility of the fluorescein film between the cornea and applaning surface. I believe that he has underestimated the magnitude of this error.

In his treatment, Dr. Moses assumes that the flattened cornea maintains the shape of a perfect sphere from which a plane segment has been cut. It seems a more reasonable assumption that the cornea behaves as a thin elastic membrane and takes up a shape determined by the forces of tension and pressure acting on it. This shape may be calculated very easily in the region very close to the applanation circle.

Let ρ be the radius of the applanation circle and consider the horizontal forces acting on a very narrow circular element of cornea between the radii ρ and $\rho + x$. The tension, T, from the adjoining cornea pulling the element to the left must be exactly balanced by the intraocular pressure, P, pushing it to the right.

The intraocular pressure exerts a force $2\pi\rho\ x\ P$ on the element, and the horizontal component of the tension is $2\pi\rho\ T\ \sin\theta$ where θ is the angle that the tangent to the cornea makes with the tonometer surface.

Accordingly:

$$Px = T \sin\theta$$

However, since θ is very small:

$$\sin\theta = \tan\theta = \frac{dy}{dx}$$

where y is the separation of the cornea from the surface, and so:

$$\frac{Px^2}{2} = Ty$$

Furthermore, pressure and tension are related to the radius of curvature of the cor-

* Moses, R. A.: Fluorescein in applanation tonometry. Am. J. Ophth., **49**:1149-1155 (May Pt. II) 1960.

nea R by the well known relationship:

$$P=\frac{2T}{R}$$

and so, finally:

$$y=\frac{x^2}{R}$$

When x is very small the equivalent expression on Dr. Moses' assumption is approximately:

$$y=\frac{\rho x}{R}$$

The significance of these formulas can be illustrated by taking the case in which the intraocular pressure would be underestimated by 20 percent, that is the diameter is overestimated by about 10 percent. Then x will be 0.15 mm., and y takes up a value of approximately 0.03 mm. in Dr. Moses' treatment and 0.003 mm. for that given here. Accordingly, the film is 10 times thinner than he predicted and it is correspondingly more likely that such an error will occur. From the figures in Dr. Moses' paper it seems that, in order to reduce the error below this value, the concentration of fluorescein in the tear film would have to be greater than about 0.05 to 0.5 percent, depending on the concentration of anaesthetic also present. In practice, these fluorescein concentrations are unlikely to be exceeded.

The result of these calculations may represent only a first approximation to the actual conditions, since they do not take into account the complex mechanical properties of the cornea. Nevertheless, it would explain, in part, why the average value of the intraocular pressure, 15.5 mm. Hg, as measured with the Goldmann tonometer, is below that, 19 mm. Hg, found by other methods†

(Signed) D. M. Maurice,
Institute of Ophthalmology,
London, England.

† Bain, W. E. S., and Maurice, D. M.: Physiological variations in the intraocular pressure. Tr. Ophth. Soc. U. Kingdom, **79**:249-260, 1959.

Dr. Moses' reply

Editor,
American Journal of Ophthalmology:

Dr. Maurice correctly states that in my discussion of fluorescein in applanation tonometry I assumed the cornea to maintain the shape of a perfect sphere from which a plane segment has been cut. He states: "It seems a more reasonable assumption that the cornea behaves as a thin elastic membrane. . . ." The cornea is not thin. Its thickness is one sixteenth of its radius of curvature and one sixth of the diameter flattened in applanation tonometry.

Dr. Maurice's mathematical treatment of his assumed thin elastic membrane is interesting but I do not see where he has demonstrated that his assumption is a more reasonable representation of the cornea.

Goldmann and Schmidt (Ophthalmologica, **134**:221, 1957) and I (Am. J. Ophth., **46**:865, 1958) have checked the calibration of the applanation tonometer against manometric pressure in fresh enucleated human eyes. I have no reason to doubt its clinical accuracy.

If the precise shape of the cornea beyond the applanated area is of interest to Dr. Maurice I would suggest that he measure it. This could be done very accurately.

(Signed) Robert A. Moses
Washington University
School of Medicine,
Saint Louis, Missouri.

* * * *

Professor Goldmann's reply

Editor,
American Journal of Ophthalmology:

To the statements of Dr. Moses I wish to add only a few remarks. Our measurements on freshly enucleated eyes have always shown a good agreement between manometric and applanation measurements. Dr. Maurice says that our results are in contradiction to the results of other methods. From his former publication (Bain, W. E. S., and

Maurice, D. M.: Physiological variations in the intraocular pressure. Tr. Ophth. Soc. U. Kingdom, 79:249-260, 1959) I conclude that Dr. Maurice means with these methods (besides his own) McBain's and Torre Estrades'. In his latest publication (Tonometer calibration. Arch. Ophth., 63:936-942, 1960) McBain concludes that his tonometric results confirm (in spite of nonvalidity of Friedenwald's P_t curve and Friedenwald's law) the validity of Friedenwald's mean P_o curve (1955). That concludes that the mean value of normal tension is around 16 mm. Hg. Torre Estrades' results (Nuevos datos para la determinacion de la media tensional del ojo humano. Actualités Latines d'Ophtalmologie. Paris, Masson, 1958, p. 160) are peculiar. He communicates in addition to his manometric values his Schiøtz values. Now there exist thousands and thousands of measurements performed in the last years with the Schiøtz tonometer (Nordmann, Weekers, Leydhecker); the mean normal value which these authors found is between 15.5 and 17 mm. Hg. The mean value of Torre Estrades' Schiøtz readings in his so-called normal material is 21 mm. Hg. So either his measurements or his material or the conditions under which his values are obtained are open to doubt.

(Signed) H. Goldmann,
University of Berne
Eye Clinic,
Berne, Switzerland.

BOOK REVIEWS

ADVANCES IN OPHTHALMOLOGY: VOLUME IX. Edited by E. B. Streiff. Basel, S. Karger, 1959. 380 pages, index for volumes I-IX. Price: Swiss francs, 56.

These excellent annual volumes have become important additions to our reference libraries and we have learned to await their appearance with eager anticipation. The latest volume (IX) contains four original papers that are small monographs and an important and most comprehensive review article, by H. Fanta of Vienna, on the lids and lacrimal apparatus (113 pages in German).

The first of the original articles is "The duplicity theory: An evaluation" by P. Saugstad and A. Saugstad of Oslo (51 pages in English). This is an excellent and unbiased paper dealing with the arguments for and against the theory of duality of function between two types of retinal photoreceptors (rods and cones). The conclusion drawn is that the theory "must be elaborated in such a way that its statements are qualified by being worked into a more comprehensive theory of the functions of the nervous structure of the retina and the whole visual system."

The second article, "Vertical strabismus," is by E. Malbran and A. Norris of Buenos Aires (57 pages in French). This is a very good résumé of the various theories (mechanical, anatomic, neurophysiologic, and neuromuscular) that should by this time be fairly familiar to the ophthalmologists of the United States, since we have been particularly active in this field for the past decade or so. Indeed, the authors lean heavily on the North American authorities. The authors conclude that, while all of the theories have some merit, none satisfies all of the requirements and so it seems necessary to evoke others that consider anomalies of development of the reflex apparatus based on an innervational mechanism. The second part of the paper is concerned with diagnosis. This is particularly good and well considered.

The third paper, "The fluorescein permeability of the blood-aqueous barrier," is by Gyula Lugossy of Budapest (41 pages in English). After a careful and critical discussion of the anatomy and physiology of the blood-aqueous barrier, the author describes the apparatus and techniques involved in fluorescein permeability and then points out the great value this determination may have in a study of a surprisingly large variety of ocular and even general diseases.

The final paper is by G. E. Jayle, A. Croisy, G. Ferrand, S. Junod, R. Boyer, and L. Aubert, Marseilles (14 pages in French) on "Electromechanographic charts in oph-

thalmology: The establishment of a standard chart (fiche) of ocular senescence." As near as I can come to what the authors are saying, this is a sort of IBM punch-card system which they believe should be adopted by ophthalmologists. As a starter they present good arguments in support of the idea and enclose samples of charts pertaining to a study of ocular senescence.

Derrick Vail.

DICTIONARY OF VISUAL SCIENCE. Edited by M. S. Schapero, B.S., O.D., David Cline, B.S., and H. W. Hofstetter, Ph.D. Philadelphia, Chilton Co., 1960. 785 pages, 96 illustrations. Price: $15.00

The more than 13,000 listings in this comprehensive glossary cover all fields that directly or indirectly pertain to vision from anatomy to statistics. The 61 collaborators include five ophthalmologists (A. Jampolsky, M. W. Nugent, J. I. Pascal, P. D. Shanedling and P. Tower), 25 Ph.D.'s, and 26 optometrists, most of whom have additional professional or university degrees. Though emphasis has been placed on the essential definition of terms, the system of listing subentries under key nouns has the value occasionally of providing some encyclopedic elaboration, as under *accommodation, amblyopia, convergence, keratitis, lens, power, telescope, reflex,* and so forth. However, in other instances, as with *angle, body, experiment, length, ring, test,* and so forth, this system is but an arbitrary convenience. Until one gets the hang of using the book the cross-references may be annoying, as *Fick's phenomenon,* see *Sattler's veil; Sattler's veil,* see *veil.* Such vexations could be avoided by printing the key word in italics or bold type. However, cross-references are preferable to entries with perfunctory definitions that do not define, as with *crossed cylinders,* though the treatment for the same term is adequate and illustrated under *lens, cross-cylinder.* Not many errors or omissions are present. Looking under *area,* Martegiani is not capitalized; Schiøtz is given, unfortunately, the usual mispronunciation (she-ots, instead of shuts); and Tuohy is not represented in the many subentries under *lens, contact.* Several esoteric, obsolete words could well be omitted such as *ophthalmiater, ophthalmiatrist* (ophthalmologist), *ophthalmiatrics* (ophthalmology), *ophthalmocace* (ocular disease), *ophthalmobrachytes* (myopia), *ophthalmomacrosis* (buphthalmos). Such pruning might provide room for brief biographic notes, now absent, on the chief contributors to visual science. *Fibroplasia, retrolental* is competently depicted but the equivalent and preferable term, retinopathy of prematurity, is not listed.

The book is up to date to a surprising degree. A satisfactory definition of almost any term that one might look up is usually there. Goldmann's applanation *tonometer* is both well described and illustrated. This reference work fills a real need for any unfamiliar word or eponymic term in the field of vision. Actually, Kenneth Ogle of the American Committee on Optics and Visual Physiology was working on such a glossary when it was learned that this dictionary was in preparation.

James E. Lebensohn.

THE OFFICE ASSISTANT IN MEDICAL PRACTICE. By Portia M. Frederick and Carol Towner. Philadelphia, W. B. Saunders Co., 1960, second edition. 407 pages, 76 illustrations, 2 appendixes, index. Price: $5.25.

Once having seen this book you can readily understand why a second edition of it has appeared within four years. Miss Frederick is instructor, medical office assisting, Long Beach City College and Miss Towner is director of special services, Communications Division, American Medical Association. George F. Lull, M.D., formerly secretary and general manager, A.M.A., has contributed a foreword, in which he points out that in "1952 survey of 5,000 physicians revealed that the physician who employs one or more aides spends 40 percent less time per patient

than does the doctor who works alone." A good "office assistant" can indeed be a jewel, a poor one can easily louse things up. The good ones are hard to find and often hard to keep for any length of time, for they often leave for greener fields either in matrimony or for an increase in salary. Sometimes it may seem that they are worth more than the doctor earns, at least in their own estimation.

The authors have given us an invaluable book based on sound experience and written in simple language with excellent illustrations. Using it as a text any bright girl can and should develop into a high-class secretary and assistant in a reasonable time. Her skills and techniques can be polished to a high luster.

This is a fine "how to" book, that should be in the hands of every office assistant.

Derrick Vail.

INDUSTRIAL OPHTHALMOLOGY. By Edward Zagora, M.D. Warsaw, Poland, Government Publishing Co., 1953. 385 pages, 166 illustrations, full bibliography, index. Price: 38 zloty

This text on industrial ophthalmology is addressed to the doctor in industry as well as to the ophthalmologist. All phases of the subject are considered. The prevention and treatment of eye injuries from light manufacturing to mining is adequately covered as well as ocular diseases induced by toxic chemicals and radiation (X-rays, microwave, atomic). Industrial ocular hygiene, screening programs, corrective and safety lenses, and malingering tests are fully described.

The reviewer is indebted to Dr. Stanley Zdziarski for the translation.

James E. Lebensohn.

OTO-NEURO-OPHTHALMOLOGY IN PEDIATRICS. A reprint from *Confinia Neurologica*, Volume 20, No. 2.

This publication consists of five "reports" which summarize current knowledge of certain aspects of oto-neuro-ophthalmic disturbances and 10 "communications" of studies of various individual problems, such as "A case of Recklinghausen's disease with ocular localization," "Cogan's syndrome," and "Neonatal exophthalmos of neoplastic origin".

F. H. Haessler.

HERITABLE DISORDERS OF CONNECTIVE TISSUE. By Victor A. McKusick, M.D. St. Louis, C. V. Mosby Co., 1959, illustrated second edition. 327 pages, 103 figures, references, index. Price: $12.00.

The author, associate professor of medicine, The Johns Hopkins University School of Medicine, brought out the first edition of this work in 1956. The steady increase in interest and contributions in the field since then has necessitated an enlarged and revised edition of this unique book, so important to those of us involved in no-matter-what aspects of medicine. The author in his preface cites Asboe-Hansen who said "connective tissue connects the numerous branches of medical science. Without connective tissue, medicine would come to pieces, even non-viable pieces, just like the cells of the human body."

After an exceedingly well-done introductory chapter on the clinical behavior of hereditary syndromes, the author goes into detailed discussions of the following syndromes: Marfan, Ehlers-Danlos, osteogenesis imperfecta, pseudoxanthoma elasticum, and Hurler syndrome. The concluding comments are embraced in a separate chapter and include a discussion of fibrodysplasia ossificans progressiva, osteopoikilos, Léri's pleonosteosis, Paget's disease of bone, and other possible hereditary and generalized disorders of connective tissue.

Most of these syndromes are of interest to the ophthalmologist who may encounter one or more at any time in his daily work. This book should be carefully studied by each of us.

Derrick Vail.

ABSTRACT DEPARTMENT

EDITED BY DR. F. HERBERT HAESSLER

Abstracts are classified under the divisions listed below. It must be remembered that any given paper may belong to several divisions of ophthalmology, although here it is mentioned only in one. Not all of the headings will necessarily be found in any one issue of the Journal.

CLASSIFICATION

1. Anatomy, embryology, and comparative ophthalmology
2. General pathology, bacteriology, immunology
3. Vegetative physiology, biochemistry, pharmacology, toxicology
4. Physiologic optics, refraction, color vision
5. Diagnosis and therapy
6. Ocular motility
7. Conjunctiva, cornea, sclera
8. Uvea, sympathetic disease, aqueous
9. Glaucoma and ocular tension
10. Crystalline lens
11. Retina and vitreous
12. Optic nerve and chiasm
13. Neuro-ophthalmology
14. Eyeball, orbit, sinuses
15. Eyelids, lacrimal apparatus
16. Tumors
17. Injuries
18. Systemic disease and parasites
19. Congenital deformities, heredity
20. Hygiene, sociology, education, and history

6
OCULAR MOTILITY

Easterly, H. D., Nadbath, R. P. and Russell, L. S. **Tendon sheath syndrome.** A.M.A. Arch. Ophth. **63**:997-1000, June, 1960.

Two cases of the syndrome first described by Brown in 1950 are presented. The typical findings were present but no surgery was done in either case because of the absence of head tilting, face turning, or untoward ocular symptoms. (2 figures, 8 references)

Edward U. Murphy.

Piper, H. F. and Holland, G. **The relationship between various passive and active qualities of movement of the eyes and their visual efficiency.** Arch. f. Ophth. **162**:8-23, 1960.

With the Ricken-Meesmann projection-adaptometer characteristic ocular movements in relation to increasing density of illumination are brought about and recorded electro-oculographically. These movements were 1. optokinetic nystagmus with moving stripes, 2. rest by fixation of a stationary mark, 3. fixation movements by fixating successively four different points at the corners of a square, and 4. movements associated with counting two rows of dots. A number of anomalous patterns of behavior are described in detail. (14 figures, 21 references)

F. H. Haessler.

7
CONJUNCTIVA, CORNEA, SCLERA

Christenberry, K. W. **Treatment of corneal abrasion with topical whole blood.** A.M.A. Arch. Ophth. **63**:948-952, June, 1960.

For the past 10 years the author has been impressed clinically with the speed of healing of corneal abrasions when a few drops of the patient's own blood are instilled into the conjunctival sac. This impression was confirmed in controlled experiments on rabbit corneas. No blood staining has been seen in over 500 patients. (6 figures, 10 references)

Edward U. Murphy.

Molnar, L. **The treatment of corneal ulcers caused by Pseudomonas pyocyanea with special attention to therapeutic keratoplasty.** Arch. f. Ophth. **162**:1-7, 1960.

Molnar reports three cases of severe

corneal infection with Pseudomonas pyocyanea. It is advisable to give broad-spectrum antibiotics after injury by foreign body or during preparation for surgery. The author recommends therapeutic keratoplasty in an early stage. (3 figures, 18 references) F. H. Haessler.

Richards, W. W. **Pseudomonas corneal infection. Case report.** A.M.A. Arch. Ophth. **63**:856-858, May, 1960.

The ulceration was successfully treated with prolonged antibiotic and steroid therapy. An 8 mm. full-thickness graft was done in the cloudy and vascularized cornea with an excellent visual result. (4 figures, 7 references)

Edward U. Murphy.

Theiler, K. and Cagianut, B. **Further data for the understanding of the Kayser-Fleischer corneal ring.** Arch. f. Ophth. **162**:66-71, 1960.

The authors add the biochemical study of the eyes of a fourth patient with Kayser-Fleischer corneal rings to the three reported in this journal four years ago. Again the studies indicated that the pigment of the corneal ring is a heavy metal. The spectographic demonstration of silver in the ring zone, the reaction of the pigment to the solvents used, and the histochemical reactions make it highly probable that silver is the metal. This study adds further evidence that Wilson's disease is associated with a disturbance of the metabolism of heavy metals. (5 figures, 2 references) F. H. Haessler.

8
UVEA, SYMPATHETIC DISEASE, AQUEOUS

François, J. and Rabaey, M. **Microelectrophoresis on agar of normal and pathological aqueous humor.** A.M.A. Arch. Ophth. **63**:836-849, May, 1960.

A technique of high voltage microelectrophoresis is described by which the protein composition of the aqueous can be examined in great detail. The normal findings are described and also those found in a few pathologic cases. (17 figures, 7 tables, 19 references)

Edward U. Murphy.

Kaufman, H. E. **Uveitis accompanied by a positive toxoplasma dye test.** A.M.A. Arch. Ophth. **63**:767-773. May, 1960.

The toxoplasmin skin test is an excellent screening test and is positive in about 95 percent of patients with positive toxoplasma dye tests. In 43 percent of patients with an active uveitis the author found complete disappearance of activity after treatment with pyrimethamine (Daraprim) and sulfonamides. (7 tables, 18 references) Edward U. Murphy.

O'Rourke, J. and Collins, Eleanor. **P^{32} localization of malignant melanoma of the posterior choroid.** A.M.A. Arch. Ophth. **63**:801-811. May, 1960.

Measurements of transscleral radiophosphorus uptake were made in eight patients after detachment of a rectus muscle during surgery. Seven had proved malignant melanoma of the posterior choroid. The tumor was localized correctly in six instances by this method and in only one by means of the transconjunctival technique. (5 figures, 2 tables, 3 references)

Edward U. Murphy.

9
GLAUCOMA AND OCULAR TENSION

Goldmann, H. **The clinical methods for the determination of the intraocular pressure and of the outflow conditions in primary glaucoma.** Ophthalmologica **139**: 214-238, March-April, 1960.

This was one of the principal reports at the annual meeting of the Swiss Ophthalmological Society in September, 1959. Addressing himself primarily to the clinician, Goldmann describes the methods

best suited for the diagnosis and follow-up of the primary glaucomas.

The distinction between angle-closure and open-angle glaucoma is made by gonioscopy during a phase of elevated intraocular pressure. If three-fourths of the angle is found closed under these conditions the diagnosis of angle-closure glaucoma is definite. If the angle is found very narrow but open to the region of the canal of Schlemm at a time when the intraocular pressure is elevated the diagnosis of open-angle glaucoma must be made. The distinction between very narrow but open angle, on the one hand, and a closed angle, on the other, is made by careful tracing, in focal light, of the optical sections of the anterior and posterior wall, after Leydhecker.

Combinations of angle-closure and open-angle glaucoma are not uncommon. Threatening (impending) angle-closure glaucoma may be recognized by unusual shallowness of the anterior chamber. There is a fairly close correlation between shallowness of the anterior chamber and narrowness of the angle but exceptions to this rule are not uncommon. The width of the angle should therefore be ascertained before any mydriatic is used for diagnostic purposes. There are no "perfectly safe mydriatics" that is, mydriatics that can be used with absolute impunity in eyes with very narrow angles. The functional significance of the narrow angle may be determined by the dark room test.

The natural history of open-angle glaucoma has been greatly clarified by Leydhecker's survey of 20,000 adults with, as far as they knew, normal eyes. This study has yielded representative figures for the incidence in the adult population of three stages of open-angle glaucoma, namely 1. the early stage with tonometric readings with the 5.5 gm. weight of four or less scale units, 2. a stage in which the diagnosis of glaucoma is based on elevated tensions, a positive response to a provocative test and positive ophthalmoscopic findings and 3. advanced glaucoma with the findings as described under 2. plus visual field defects exceeding arcuate scotomas. Plotted against the age of the individual the logarithms of the absolute numbers in catagories 2. and 3. give straight lines. This defines open-angle glaucoma as a slowly progressive disease in which the intraocular pressure at first rises without causing any subjective symptoms and, after a period of years, causes characteristic disc and field changes.

In the office practice of ophthalmology open-angle glaucoma must be suspected in every adult and is diagnosed by tonometry and ophthalmoscopy.

Goldmann stresses the limits of tonometry with a Schiøtz tonometer. It gives a reading in every case without indicating in which type of case this reading is a reliable estimate of the intraocular pressure and in which case it is not. The Schiøtz tonometer is likely to give unreliable readings in conditions such as macrocornea, microcornea, high degrees of myopia, and after certain types of ocular surgery.

Applied to the average, not highly myopic eye which has not been operated upon, a standardized tonometer is "a pretty good" instrument for estimation of the intraocular pressure, if several readings are taken with different weights. "Unfortunately there are not many such instruments available nor are there many ophthalmologists who routinely make such measurements." There is no justification for the use of impression tonometers other than the standard Schiøtz instrument because no other instrument has been standardized as carefully and used as extensively in calibration studies.

The earliest ophthalmoscopic changes in open-angle glaucoma are due to atrophy of prelaminar tissue. In cases with pre-existent anomalies, such as a very

oblique exit of the optic nerve, the glaucomatous atrophy does not lead to the picture of the typical excavation.

The diurnal variations of the intraocular pressure are of great diagnostic value. Large diurnal variations are often a sign of angle-closure glaucoma. In open-angle glaucoma the peak is usually reached in the early morning hours. Goldmann strongly recommends tensions taken at 7:00 a.m. before the patient gets out of bed. "I don't see why the ophthalmologist should not make house calls, just like the internist or the general practitioner."

Only two provocative tests are of real significance, the mydriasis test in angle-closure glaucoma and the water-drinking test in open-angle glaucoma. Tonography is still based on too many assumptions to be of practical value in the diagnosis or follow-up of glaucoma. (6 figures, 30 references) Peter C. Kronfeld.

Heinzen, H. and Leuder, P. **The value of gonioscopy in the diagnosis of pigment glaucoma.** Ophthalmologica **139**:244-254, March-April, 1960.

The report concerns nine cases of pigment glaucoma (or Scheie's idiopathic atrophy of the epithelial layer of iris and ciliary body) with excessive deposition of iris pigment in the midtrabecular zone (well shown in a gonio-photograph). (4 figures, 40 references)

Peter C. Kronfeld.

Kruse, Wolfgang. **A new method for determining the rigidity coefficient.** Arch. f. Ophth. **162**:78-96, 1960.

This author prejudices the abstractor in his favor by expressing his facts and opinions directly, clearly, and unequivocally. He numbers his references and his illustrations really illustrate. He makes his measurements with the aplanation tonometer in which he uses prisms of various sizes. The median coefficient of rigidity was found to be slightly greater than Friedenwald's average value. The half-logarithm formula was found to be adequate for clinical use but is not valid at low-pressure levels. With increasing levels of pressure a reduction of rigidity becomes manifest; for this reason a statement of average rigidity coefficients should be accompanied by a notation of average tension. (8 figures, 5 tables, 46 references) F. H. Haessler.

Lavel, Joseph. **Results of surgery in patients with tubular fields due to glaucoma.** A.M.A. Arch. Ophth. **63**:850-852, May, 1960

The author strongly advises against the widely held opinion that it is dangerous to operate on patients with small central fields and uncontrolled tension. Without surgery they will lose what vision remains. Not one of the 15 patients reported here lost central vision after operation. (1 table, 5 references)

Edward U. Murphy.

McBain, E. H. **Tonometer calibration. III. Volume of indentation and P_o determination.** A.M.A. Arch. Ophth. **63**:936-942, June, 1960.

Measurements on enucleated eyes of the volume of indentation by the Schiøtz tonometer were made and compared with those previously found in the 1955 calibration. The new results were higher as were also those for the facility of aqueous outflow when calculated from these data. Agreement was close however for pressure in the undisturbed eye. (4 figures, 6 tables, 8 references)

Edward U. Murphy.

Redslob, E. **The prognosis of chronic glaucoma.** Ann. d'ocul **193**:446-450, May, 1960.

A finding of ocular hypertension does not invariably mean a loss of central vision or of visual fields. The author cites

several cases in which good central vision and intact visual fields have been maintained for many years in spite of repeated elevation of the ocular tension. He emphasizes that in chronic (open-angle) glaucoma one should not be hasty about reducing the ocular tension by surgery since the latter produces many complications and is unnecessary if visual function remains intact despite elevated pressures. David Shoch.

Rocha, H. and Calixto, N. **Observations on tonography.** Arq. brasil. de oftal. 22:301-354, 1959.

In clinical practice tonometry and campimetry are the essential examinations for the diagnosis, prognosis and therapy of glaucoma. Tonography, however, is a valuable source of information, but remains as a field which should be reserved for research rather than clinical practice. The authors review the theory of tonometry and tonography and discuss applanation tonometry as contrasted to the conventional method.

Tables of data, charts and mathematical formulae constitute the major portion of the article. There are discussions of scleral rigidity, variations in the volume of ocular content during tonometry, facility of outflow and the Friedenwald nomogram. (10 figures, numerous charts, 25 references) James W. Brennan.

Schmidt, T. **A routine procedure for the early diagnosis and follow-up in chronic simple glaucoma.** Ophthalmologica 139:265-270, March-April, 1960.

A procedure worked out by the University Eye Clinic in Berne, Switzerland for the recognition and management of early chronic simple glaucoma is described in detail. The principal tools are Goldmann's applanation tonometer and his perimeter. The two major unknowns with regard to chronic simple glaucoma are 1. the statistical distribution of intraocular pressure values in a glaucoma population and 2. the pressure level at which optic nerve damage begins to occur. The pressure values of the normal and the glaucoma population most likely overlap to some extent. Pressure damage may be assumed to occur from a level of 24 mm. Hg upward, with, in all probability, marked individual variations.

Every clinic patient over 40 years of age and every myope of more than three diopters and over 20 years of age is examined with the applanation tonometer at least once a year. Readings over 21 mm. Hg call for visual field examination. In cases of tensions up to 24 without field changes the next step is the determination of the diurnal variations. This is done largely in the outpatient department, but for the 7:00 a.m. reading the patient is usually admitted to the hospital. Great emphasis is placed on this 7:00 a.m. reading which is taken with the Schiøtz tonometer in the patient's bedroom in the dark and prior to any of the usual early morning activities, that is, with the patient still in a state of rest but not necessarily asleep.

Repeated pressure readings of more than 22:5 mm. Hg call for treatment with pilocarpine. The treatment is considered adequate if the pressure readings on at least two different days are below 20 mm. Hg and if the visual fields tested every four months remain stationary. The water-drinking test which is the only provocative test used, is employed in cases of discrepancies, such as positive field findings and negative diurnal pressure findings. The resistance to aqueous outflow is measured very rarely. (2 figures) Peter C. Kronfeld.

Streiff, E. B. and Stucchi, C. **Treatment of glaucoma by destruction of the ciliary arteries.** Ophthalmologica 139:262-265, March-April, 1960.

Favorable results have been obtained in primary and secondary glaucomas by surface diathermy applied to the sclera directly behind the insertion of from two to four rectus muscles. The tendon is secured with catgut sutures and severed at its insertion; an area of sclera, measuring three to seven millimeters, is diathermized with a flat electrode and the tendon is reattached. The epibulbar tissues are closed carefully. In the beginning the authors operated only on the two horizontal rectus muscles. If the result was insufficient the same procedure was carried out as a second step at the insertions of the vertical recti.

The results seemed to be better if all four rectus muscles were "treated" in one sitting. Repeated applanometric readings below 22 mm. Hg are the criterion of success of the operation. No serious complications of any kind have been observed. The cornea becomes slightly hypesthetic, the chamber angle remains open, and the motility essentially normal. The operation may cause a considerable degree of astigmatism which is easily correctable with glasses.

"This surgical technique should be considered in every case of glaucoma and particularly when there is severe field loss right up to the point of fixation. The operation entails very little trauma and practically no risk." (1 table, 13 references) Peter C. Kronfeld.

Valu, L. and Csüllög, F. **Surgical problems connected with operations for glaucoma simplex and their results.** Szemészet 97:70-77, 1960.

If possible, eyes with glaucoma simplex must not be operated on at the first observation of the disease, because in spite of the increased intraocular pressure the eye functions do not show any deterioration in very many of the patients. In cases with a pressure lower than 40 mm. Hg he recommends cyclo-anaemisation; with pressure more than 40 mm. Hg he does a peripheral iridectomy if the operation seems to be quite inevitable.

Gyula Lugossy.

Varga, M. **Action of lytic cocktail in acute glaucoma.** Szemészet 97:97-100, 1960.

The observations made with lytic cocktail on 50 patients with glaucoma are discussed. This therapy results in the lysis of the glaucoma attack and secures favourable conditions for operation.

Gyula Lugossy.

Wagner, T. **Experiences with two more recent operations for glaucoma (Malbran's filtering iridectomy and Weekers' cyclodiathermy type 2).** Ophthalmologica 139:255-261, March-April, 1960.

Bangerter's clinic in St. Gallen reports its results with Malbran's filtering iridectomy (cfr., Am. J. Ophth. 47:34, 1959). The principal indication was narrowness of the angle in either open-angle or closed-angle glaucoma. In a series of 25 such eyes the operation succeeded in normalizing the ocular tension without miotics in 15 and with miotics in another six eyes. The operation appeared to accomplish as much as the iridencleisis does.

Weekers' cyclodiathermy type 2 aims at reduction of the arterial blood supply to the ciliary body. The applications of diathermy are made with a flat electrode directly in front of the insertions of the horizontal rectus muscles and ligatures are placed around the tendon of the muscle in order to reduce the flow in the anterior ciliary arteries. Remarkably good results are reported in 27 out of a group of 35 eyes with conditions such as far-advanced open-angle glaucoma, aphakic eyes with much vitreous in the anterior chamber, rubeosis of the iris, and obstruction of the central retinal vein. (5 figures, 5 references) Peter C. Kronfeld.

10
CRYSTALLINE LENS

Murray, R. G. and Drance, S. M. **The use of alpha-chymotrypsin in cataract surgery.** A.M.A. Arch. Ophth. **63**:910-917, June, 1960.

Two hundred cases without the use of the enzyme are compared carefully and thoughtfully with 42 cases in which it was used. All facets of the surgery and postoperative complications were examined and the authors conclude that a considerably higher percentage of complications was found in the enzyme group. However, in the age group between 40 and 60 years, the complications were significantly less with the enzyme than without. The authors suggest that its use be reserved for those cases where difficulty is anticipated in doing an intracapsular extraction. (8 tables, 9 references)

Edward U. Murphy.

Silveira, F. **Phakoeresis of Barraquer.** Arq. brasil de oftal. **22**:293-300, 1959.

The author reports his observations in a series of 40 cataract extractions with alpha-chymotrypsin and phakoeresis according to the technique of Barraquer; 35 lenses were delivered intracapsularly. There is no statistical report of final visual acuity.

The "lytic cocktail" was used to potentiate local anesthesia. A Graefe knife section with a conjunctival flap is preferred, followed by peripheral iridectomy and instillation of the chymotrypsin. Extraction is done with Barraquer's erisophake after which the anterior chamber is irrigated with a solution of acetylcholine for miosis. Virgin silk on small Grieshaber needles is used for closure of the wound.

The author recommends this technique since it appears to facilitate the intracapsular extraction and allows early ambulation of the patient. There is an almost complete lack of vitreous hemorrhage, although the incidence of striate keratitis is high, and three cases of corneal dystrophy were observed. The potentiated anesthesia affords a tranquility to the entire procedure. (6 references)

James W. Brennan.

11
RETINA AND VITREOUS

Curtin, V. T., Norton, E. W. D. and Smith, T. R. **Pathological confirmation of retinoschisis.** A.M.A. Arch. Ophth. **63**: 978-983, June, 1960.

A patient with a choroidal malignant melanoma showed retinoschisis bilaterally. The enucleated eye was studied histologically and the retinoschisis described. It was represented by a cystic area bounded by the outer nuclear layer externally and the nerve fiber layer internally. There were many resemblances to peripheral cystoid degeneration of the retina. (9 figures, 7 references)

Edward U. Murphy.

Dollfus, M.-A., and Raeymaeckers, G., **Galvanocautery with a fine-tip electrode in the treatment of detachment of the retina and a study of 1060 cases.** Ann. d'ocul. **193**:385-409, May, 1960.

A thirty-year survey of retinal detachment is presented. The total number of cases studied was 1,060 and valuable data are tabulated as to refractive error, age, site of tears, number of tears, etc. in this group. In approximately 10 per cent trauma was the etiologic factor. Only two methods of surgical treatment are reported. These are diathermy coagulation and galvanocautery. Of the entire group of detachments, 749 cases were treated surgically and the two techniques gave about equal rates of cure; approximately 60 per cent with each method. The authors prefer galvano-cautery however, because the recuperation time is less. Bilateral detachments occurred in 10 per

cent of the total group and here the cure rate was only 47 per cent. (7 figures)

David Shoch.

Gaipa, M. **A case of nevoid pigmentation of the retina.** Arch. di ottal. **64**:23-26, 1960.

This is a case report of grouped pigmentation or melanosis of the retina and its differential diagnosis. (1 figure, 13 references) Paul W. Miles.

Klein, B. A. **Annual reviews. Retina and optic nerve.** A.M.A. Arch. Ophth. **63**: 862-900, May, 1960.

The literature for 1959 is discussed. (303 references) Edward U. Murphy.

Johnson, Sven. **Retinopathy and nephropathy in diabetes mellitus.** Diabetes **9**: 1-8, Jan.-Feb., 1960.

Controversy still rages over the influence of control of diabetic hyperglycemia on the development of vascular complications. The present study adds fuel to the argument that good control is effective in delaying the onset and reducing the severity of retinopathy and nephropathy. Two groups of patients are compared: the first (56 patients), under strict dietary regulation with accurate insulin coverage, an effort being made to prevent glycosuria; the second (104 patients), on a free diet, little attention being paid to glycosuria in the absence of ketonuria, and consequently on somewhat less strict insulin coverage. The frequency of nephropathy was dramatically lower in the first group despite an average longer duration of the disease of five and one-half years! No significant difference in frequency of mild retinopathy was found, but severe retinopathy and severe impairment of vision was significantly greater in the second group, despite the much shorter duration of their diabetes. In addition, the far better weight control and the greater frequency of insulin treatments (and reactions) in the first group strengthens the impression that control of the hyperglycemia was responsible for the differences in vascular complications between the two groups.

Lawrence T. Post.

Molnár, L. **ERG in degeneratio pigmentosa retinae, before and after treatment.** Szemészet **97**: 101-103, 1960.

In hereditary cases the "dead" wave found before treatment did not change, although the treatment resulted in improvement. If a c wave was found, therapy was followed by the appearance of a subnormal b wave. This is, beside the cessation of complaints, an objective sign of nearly normal functions and reactivity of the retina, thus the ERG can be the basis of prognosis in similar cases.

Gyula Lugossy.

Pope, C. H., Jr. **Retinal capillary microaneurysms: a concept of pathogenesis.** Diabetes **9**:9-10, Jan.-Feb., 1960.

The pathogenesis of retinal capillary aneurysms in diabetes is not as yet clearly understood. The author tries to clarify this problem by the application of various stains to serial, tangential sections of flat preparations of the retina. Four normal and four diabetic retinas are studied; the reticulin stain of Wilder and the PAS mucoid stain were found most useful. The normal capillary consists of a multi-layered PAS-staining basement membrane, lined internally by flattened endothelial cells, and externally by a reticulin network. The reticulin network is not observed over the surface of capillary aneurysms, indicating a dehiscence in this supporting structure. In diabetics lipid material is observed in the lumina and the endothelial cells of the capillaries and in the walls of the aneurysms; none is seen in normal capillaries. The following pathogenesis is suggested: the high concentration of serum lipids character-

istic of diabetes lead to absorption of these lipids by capillary endothelial cells; consequent swelling of these cells causes separation of reticulin fibers, allowing outpouching of the basement membrane and endothelium through the weakened area. The predilection for the retina is ascribed to the normally high intracapillary pressure of the retina, the venous stasis typical of diabetic retinopathy, and the lack of surrounding tissue support.

Lawrence T. Post.

Tusini, A. and Bergonzini, R. **Roentgen therapy of the cervico-dorsal sympathetic chain in retinitis pigmentosa. A clinical study of the changes in light perception and the field of vision.** Riv. otoneuro-oftal. **35**:149-161, March-April, 1960.

The authors review the literature concerning previously reported approaches to the therapy of retinitis pigmentosa. They then describe the effect of X-ray therapy to the cervicodorsal sympathetic chain in 14 patients with retinitis pigmentosa. The authors achieved good results; an improvement in the visual field and in the visual acuity and light sense were obtained in 76 percent of these patients. They emphasize that early Roentgen therapy is necessary for an effective result. This form of treatment should preferably take place while there are still reversible vascular changes. (2 tables, 22 references) Wm. C. Caccamise.

Vörösmarthy, D., Földes, I. and Darabos, G. **Persisting hyperplastic primary vitreous body.** Szemészet **97**:10-16, 1960.

Two cases are reported; the condition was recognized in one patient after enucleation and in the other before operation. Histologically a thickened membrana limitans interna with connective tissue, a persisting hyaloid artery and a retrolenticular tissue mass were found. The authors believe that the preretinal tissue corresponds to the thickened membrana limitans interna.

Gyula Lugossy.

Vos, T. **Persistent hyperplasia of the primary vitreous.** Rev. brasil. oftal. **19**: 117-126, June, 1960.

In 1936 the author published an article about eyes which had been enucleated with the diagnosis of pseudoglioma. When the data were reviewed in the light of Reese's work on hyperplasia of the primary vitreous, it was found that some of these lesions should be diagnosed as such. The author then describes the embryology of the vitreous, the clinical features of persistent primary vitreous, and the differential diagnosis. Walter Mayer.

12

OPTIC NERVE AND CHIASM

De Vincentiis, M. and Gaipa, M. **A case of black optic disc.** Arch. di ottal. **64**:27-29, 1960.

A nine-year-old boy had a history of forceps injury of one eye at birth. The other eye had normal vision. The injured eye was blind and diverged outward 30 degrees. The anterior segment appeared normal, but the optic disc was gray and surrounded by a white scleral scar. There were black pigment spots on it and a physiologic excavation was present. The vessels were displaced. The macula showed degeneration. X rays of the optic foramen were negative.

A forceps injury of the optic nerve was assumed, but a congenital malformation could not be ruled out. (1 figure, 4 references) Paul W. Miles.

Gaipa, M. **Observations on some cases of coloboma of the optic disc.** Arch. di ottal. **64**:5-10, 1960.

Four patients are described in whom the coloboma must have originated during the formation of the optic cup in early embryonic life. All but one had

good vision. One child, eight years of age, had a deep excavation of one disc with microphthalmos, esotropia, and persistent hyaloid artery. A woman, 48 years of age, had white discs with an excavation four diopters deep suggesting glaucoma. A 13-year-old boy had one disc excavated 20 diopters. (7 figures, 7 references)

Paul W. Miles.

Kennedy, Charles. **Optic neuritis in children.** A.M.A. Arch. Ophth. **63**:747-755. May, 1960.

The author studied 41 patients from four to 15 years of age. The neuritis differed from that in adults in having a greater tendency to simultaneous bilateral involvement, or greater frequency of headache, and almost constantly a greater frequency of papillitis rather than retrobulbar neuritis. Over half of the neuritides were of unknown etiology, eight of the patients had multiple sclerosis, six had systemic disease, four hereditary optic atrophy, and one had Schilder's disease. A variety of treatment was used for the neuritides of unknown etiology but their value was questionable since all of the untreated cases also showed marked improvement. (9 tables, 36 references)

Edward U. Murphy.

Rein, Gerhard. **Melanoblastoma of the papilla and tumors of the retinal pigment epithelium.** Arch. f. Ophth. **161**:519-531, 1960.

The left eye of a 55-year-old man was enucleated because of an extremely rare primary melanoblastoma of the papilla. Surprisingly, histologic study revealed the presence of neurogenic elements. A melanoblastoma of this type has not been observed in this location before. The author presents convincing evidence that the cells of the tumor originated in the retinal pigmented epithelium. (5 figures, 41 references) F. H. Haessler.

Scardovi, C. **Quadrantopsia in a case of colobomatous pitting of the optic disc.** Riv. oto-neuro-oftal. **35**:199-203, March-April, 1960.

The author points out that although colobomatous pitting of the optic disc has not been reported very frequently, it is not extremely rare. His review of the literature revealed approximately 80 case reports. This congenital condition is usually unilateral and occurs more frequently in females. It is usually located in the inferior temporal quadrant of the disc. The visual acuity is usually not significantly affected. The author presents the findings in a 56-year-old woman. The visual acuity was correctible to 20/20 in each eye. Ophthalmoscopic examination revealed a grossly triangular excavation in the inferior temporal sector of the optic disc of the left eye. The depth of the depression measured approximately 3 diopters (1mm.). Visual field studies revealed no abnormality in the right eye. However, in the left eye, a superior nasal quadrant defect was detected. Treatment with vasodilators for 15 days produced no change in the field defect. The author therefore concludes that the field defect can be attributed to the anatomic lesion of the optic disc. (2 figures, 12 references)

Wm. C. Caccamise.

Zülch, K. J. and Nover, A. **The spongioblastomas of the optic nerve.** Arch. f. Ophth. **161**:405-419, 1960.

The authors studied 29 primary neoplasms which originated in the glia of the optic nerve. They describe details of microscopic structure such as the architecture in general, regressive manifestations, infiltration of the arachnoid sheath and the septa, and the ground substance of the fascicular opticus. In the biologic characterization age of patient, relation to sex, the low degree of malignancy, and rate of growth are noted. Postoperative survival was over ten years in some pa-

tients and among 16 patients who were treated surgically, a recurrence was noted but once.

In the morphologic as well as clinical data many characteristics are comparable to those of spongioblastomas of the central nervous system. These lead the authors to suggest that these neoplasms be referred to as spongioblastomas. (12 figures, 42 references) F. H. Haessler.

13
NEURO-OPHTHALMOLOGY

D'Orio, R. and Millefiorini, M. **Trigeminal-ophthalmoplegic syndromes of obscure origin.** Riv. oto-neuro-oftal. **35**:186-195, March-April, 1960.

The authors point out that very frequently in neuro-ophthalmology one is confronted with syndromes that are characterized by involvement of one or more oculomotor nerves and disturbances in the areas innervated by the trigeminal nerve. They present the case histories of five patients with trigeminal-oculomotor syndromes in whom a definite etiologic factor could not be determined and then discuss the various possible causes of simultaneous involvement of the third and fifth cranial nerves. (8 references)

Wm. C. Caccamise.

Fanta, H. **The visual field for stationary and moving white stimuli in intracranial processes.** Arch. f. Ophth. **161**: 492-501, 1960.

The differences between the visual field for a white moving object and for white as a color are clearly recognizable with intracranial abnormalities, particularly with space-occupying lesions, and are easily recorded. With direct injury to the optic nerve or tract this discrepancy is less striking. (11 figures, 10 references)

F. H. Haessler.

Harrison, M. and Parker, N. **Congenital facial diplegia.** M. J. Australia **1**:650-653, 1960.

Seven cases of congenital facial diplegia are described and the characteristic features are tabulated. Other neuro-muscular defects were common. Sixth nerve palsy was present in four cases. This palsy had the following distinctive characteristics: neither eye could be abducted beyond the mid-line and there was paralysis of horizontal conjugate movement. Horizontal nystagmus could not be provoked by caloric or rotatory tests. Two patients were cousins and one was from a consanguineous marriage.

Ronald Lowe.

Keefe, W., Rucker, C. and Kernohan, J. **Pathogenesis of paralysis of the third cranial nerve.** A.M.A. Arch. Ophth. **63**:585-592, April, 1960.

A few representative examples of the commoner causes of oculomotor nerve paralysis are discussed and the autopsy findings presented. The cases include head injury, pontine hemorrhage, cerebral edema, cerebral aneurysm, brain tumor, and frontal lobe abscess. The causes vary widely, but the mechanisms by which the lesions are produced in the nerves and the sites of interruption are common to many of the causes. (6 figures, 7 references)

Edward U. Murphy.

Kragh, L. V., Soule, E. H. and Masson, J. K. **Neurofibromatosis (Von Recklinghausen's disease) of the head and neck: Cosmetic and reconstructive aspects.** Plast. & Reconstruct. Surg. **25**:565-573, June, 1960.

The authors reviewed the records of 47 patients from whom neurofibromatosis tissue had been removed from the head and neck during the years 1945-1957 at the Mayo Clinic. Attempts were made to excise or partially excise large neurofibromatosis masses and to reconstruct the parts involved to as near normal contour and function as possible.

These surgical procedures helped to prevent these patients from becoming social cripples. Trauma from surgery has been suggested in the past as a possible etiologic factor in the malignant conversion of these tumors; on the basis of this theory some have advised against molesting these tumor masses. At the Mayo Clinic this theory has been ignored and evidence is presented that surgery of these tissues is unlikely to result in sarcomatous changes. Alston Callahan.

Metz, L. N. and Magee, K .R. **Postencephalitic blepharospasm.** A.M.A. Arch. Ophth. **63**:692-698, April, 1960.

The brain of a 61-year-old patient with severe postencephalitic blepharospasm was examined histologically. Gliosis and atrophy of nerve cells were found in the substantia nigra and, to a lesser extent, in the globus pollidus and putamen. No changes were found in the facial motor nucleus, the facial area of the motor cortex, or in the corticobulbar pathways. (1 figure, 33 references)

Edward U. Murphy.

Pasino, L. **The integrity of sensory-motor coordination in amblyopia without strabismus.** Riv. oto-neuro-oftal. **35**:162-167, March-April, 1960.

The author summarizes the results in his study of 29 patients with amblyopia. In seven of these patients the amblyopia was bilateral and each patient had foveal fixation without strabismus. The patients with amblyopia without strabismus had adequate sensory and motor coordination. From these observations the author feels that there is a different etiologic basis in amblyopia with strabismus than in amblyopia without strabismus. (1 table, 8 references) Wm. C. Caccamise.

Smith, J. L. and Cogan, D. G. **Optokinetic nystagmus in cerebral disease.** Neurology **10**:127-137, Feb., 1960.

The exact diagnostic importance of optokinetic nystagmus in the localization of cerebral lesions is not clear in the minds of most clinicians. The authors present evidence which strongly suggests that parietal lobe involvement is necessary for the appearance of abnormal (asymmetric) optokinetic nystagmus. "Asymmetric" optokinetic nystagmus refers to a significant difference in the nystagmus induced by rotation of the stimulating drum to one side as opposed to the other. Lateralizing significance of the direction of the abnormality is happily disregarded. The case histories of 14 patients (selected for adequacy of pre- and post-mortem observations) are presented. Three patients demonstrated symmetric optokinetic nystagmus and were found to have frontal, temporal, and occipital lobe lesions respectively. Six patients had asymmetric nystagmus, and all had parietal lobe involvement. The five remaining cases presented difficulties in interpretation but did not appear significantly to disturb the basic concept: that the absence of asymmetric optokinetic nystagmus appears reliably to exclude the parietal region as the site of a lesion causing homonymous hemianopsia.

Lawrence T. Post.

Stephenson, R. W. **Paralysis of accommodation with recovery after five years.** Brit. J. Ophth. **44**:51, Jan., 1960.

A 10-year-old boy developed complete bilateral paralysis of accommodation for which no reason was found. This remained unchanged for five years and then suddenly healed completely for no apparent reason. He was otherwise quite normal. Morris Kaplan.

Weigelin, E., Niesel, P. and Konstas, T. **Dynamometric study of the relationship between cerebral disturbance and cerebral circulation in the hypertonic.** Arch. f. Ophth. **161**:605-614, 1960.

The relationship between the hypertensive symptoms and circulatory blood in the cerebral vessels was studied in 50 hypertonic patients by comparing the blood pressure in the brachial and the ophthalmic artery. The statements of the patient on the changes in discomfort during a four-weeks course of therapy with hydergin were related to the systolic caliber of the cerebral vessels. Therapeutic dilation of the vessels was accompanied by increased comfort. All relationships were evaluated by routine methods of correlation statistics. (2 figures, 1 table, 20 references) F. H. Haessler.

14
EYEBALL, ORBIT, SINUSES

Caffi, M. and Paganoni, C. **Hemangiocytoma of the orbit.** Rassegna ital. d'ottal. **28**:303-309, July-Aug., 1959.

The hemangiocytoma is the more frequent type of orbital neoplasm, and is usually grouped into two forms, one of which is composed of polymorphic cells in a vascular bed, whereas the second form arises from specific constituents of the vessels. The classification is not a rigid one for at times all of the different elements are found in a single case. Tumors of this type are considered to be benign and may remain unchanged or may even regress. The patient described was a 37-year-old man who showed slight exophthalmos but no diplopia. Aspiration of orbital tissue revealed the type of cells; as much tissue as possible was aspirated. E. M. Blake.

Csepi, K. **Factors contributing to the development of endocrine exophthalmos.** Szemészet **97**:1-9, 1960.

The author examined 72 patients with endocrine exophthalmos which he ascribed to unfavourable environmental effects acting through the nervous system. The majority of patients were constantly irritated because of professions in which they had much work with great responsibility and little system; 91.6 percent were city inhabitants, and only 8.4 percent lived in villages. In 84.6 percent the onset of the deterioration of exophthalmos coincided with the operative or medicamentous reduction of thyroid function. The percentage of postoperative exophthalmos was especially high: 77.7 percent. The time elapsing between the strumectomy and the development of exophthalmos ranged between one day and 13 years. In 62 percent of the patients diminished function of the gonads was found. Gyula Lugossy.

François, J. and De Vos, E. **Intraparietal meningocele of the orbit.** Ann. d'ocul. **193**:289-297, April, 1960.

A nine-year-old girl showed a left nonpulsating exophthalmos, paralysis of the lateral rectus and an enlargement of the orbit. A surgical approach via the lateral orbital wall exposed a thin orbital bone and beneath this a thin membrane. Incision of this membrane released a watery fluid which spurted out synchronously with the pulse.

The authors conclude that this was a large meningocele which invaded the orbit via the superior orbital fissure to form a "collar-button" cyst. (7 figures, 30 references) David Shoch.

Herzensderfer, A. **Plastic surgery of the orbit.** Ophthalmologica **139**:115-119, Feb., 1960.

The author compares his procedure with that of Csapody and finds his more certain to succeed. (2 figures, 6 references) F. H. Haessler.

Mordhorst, C. H. **Orbital cysts.** Acta ophth. **38**:163-169, 1960.

Five cases of orbital cysts are discussed from a clinical, surgical and histological point of view. The diagnoses were 1. hematic cyst, 2. dermoid cyst, 3. epithelial

cyst, and 4. cystic adenoid epithelioma. The frozen-section technique is indispensable for diagnosis at the time of operation. (5 figures, 15 references)

John J. Stern.

15
EYELIDS, LACRIMAL APPARATUS

McLaren, D. S. **Kaposi's sarcoma of the eyelid of an African child.** A.M.A. Arch. Ophth. **63**:859-861. May, 1960.

A case is reported in a two-year-old child in whom improvement followed local excision. The diagnosis was confirmed histologically. (4 figures, 6 references) Edward U. Murphy.

Németh, L. **Blepharophimosis and its surgical treatment.** Szemészet **97**:82-87, 1960.

Blepharophimosis is a well defined picture which has different forms. It must be differentiated from epicanthus. The choice of therapy is operative and based on the cause since the usual canthotomies and canthoplasties are not suitable. For the senile type an operative procedure is recommended which brings about the normal site of the outer corner of the eye and the normal shape of the eyelid by three factors. By an oval incision the enlarged skin of the outer corner of the eye is shortened. The slackened ligament of the outer corner of the eye is carried out to the periosteum of the edge of the orbit by a sliding suture and fixed there. At last, by temporalward shifting the skin of the corner of the eye and pressing it against the fascia temporalis by three mattress-sutures, a stratified adhesion is achieved and an eventual slackening can be prevented. The operation gives both cosmetically and functionally a perfect and final result. Its execution is easy, there are no complications to be feared and it can be recommended. Gyula Lugossy.

Segers, A. M. and Kaminsky, A. **Treatment of lid carcinoma with radium needles.** Arch. oftal. Buenos Aires **34**:261-264, Oct., 1959.

Short (1 to 2-cm.) needles, with a radium loading of 0.66 mg. per cm. of useful length in a 0.5 mm. thick platinum case, were inserted under the palpebral skin along the ciliary border for as long as one week, in 28 patients with carcinoma of the lower lid or the inner canthus. The affected lid was drawn downward by a traction suture in order to protect the eyeball from gamma radiation. In 17 out of the 20 cases which could be followed up for at least three years, a permanent cure was achieved; in none did any lens opacities develop during that period. (3 figures) A. Urrets-Zavalía, Jr.

16
TUMORS

Blatt, N. and Ursu, A. **Malignant degeneration of an angioreticuloma of the orbit.** Arch. f. Ophth. **162**:53-65, 1960.

This tumor which developed with the utmost rapidity occurred in a four-year-old child. The malignancy of the lesion was clinically recognizable on the basis of unusual extension and most rapid growth of the tumor accompanied by cachexia, conspicuous pain in the eye, orbit and head, and the extreme youth of the patient. The disturbance began as a benign angioreticuloma which later degenerated as a result of factors which could not be determined. In the clinical differential diagnosis the roentgenograms were of valuable help. (14 figures, 21 references) F. H. Haessler.

Tsukahara, Isamu. **A histopathological study on the prognosis and radiosensitivity of retinoblastoma.** A.M.A. Arch. Ophth. **63**:1005-1008, June, 1960.

The author analyzed the data on 150 patients. The mortality was less in the well differentiated than in the mixed and less differentiated groups. Most deaths occurred within two to three years from

the last treatment and invasion of the optic nerve was found to be the most serious complication. (5 tables, 6 references) Edward U. Murphy.

Vörösmarthy, D. **Extirpation of melanoma of the eyeground by solar cauterization.** Szemészet **97**:87-89, 1960.

The malignant melanoma extirpated by solar cauterization was a juxtapapillary intraocular tumor. The method devised by the author was applied. Of all intraocular tumors, melanoma is, on account of its pigment content, the most appropriate object for photo-coagulation procedures.

Gyula Lugossy.

17
INJURIES

Goldberg, J. L. **Conjugated estrogens in the prevention of secondary hyphema after ocular trauma.** A.M.A. Arch. Ophth. **63**:1001-1004, June, 1960.

Sixty-three consecutive patients with traumatic hyphema were treated in a similar manner except that 22 received Premarin (Ayerst) intravenously on admission and orally over the next few days. Of the control group 29 percent had secondary hemorrhage and in two thirds of these glaucoma and blindness resulted. There was no secondary bleeding in the group receiving conjugated estrogens. Further studies to evaluate the value of such therapy seem indicated. (31 references) Edward U. Murphy.

Pirruccello, Frank W. **Observations in the management of soft tissue injuries of the face: The reconstruction of eyebrows.** Plast. & Reconstruct. Surg. **25**:584-594, June, 1960.

To replace lost eyebrows and tissue of the forehead, the author recommends three methods: 1. full thickness hair bearing grafts (from behind the ear opposite to the injury immediately following the accident; 2. full thickness hair-bearing grafts as a secondary procedure after the original area of injury has healed or been grafted, thus making it an elective procedure; and 3. hair-bearing arterial peninsular scalp flaps based on the superficial temporal artery when much tissue to compliment esthetic restoration is necessary. Two such cases are shown.

The article is illustrated with 21 pictures (no drawings) and a plea is made to construct a secondary vertical windshield of plastic laminated transparent material in automobiles.

Alston Callahan.

Walsh, F. B., McMeel, J. W. and Neetens, Adolf. **Fractures of the skull: ophthalmological significance.** New York Acad. Med. Bull. **36**:238-262, April, 1960.

This is an introduction to a much broader project to be undertaken by the authors, who will attempt eventually to shed more light on the blood supply to the visual pathways in health and disease. The first part of the present paper is devoted to a discussion of the pertinent anatomy, and the second part to topical, diagnostic features of fractures of the skull and orbits. The paper does not lend itself to abstracting. It is a discursive review, containing some pithy observations, but the complex nature of the subject, due to the wide variation of possible injuries, makes it difficult to assimilate in any sort of organized fashion.

Lawrence T. Post.

18
SYSTEMIC DISEASE AND PARASITES

Foerster, H. C. **Mycosis fungoides with intraocular involvement.** Tr. Am. Acad. Ophth. **64**:308-313, May-June, 1960.

A case of mycosis fungoides is presented which was followed for 15 years, and which resulted in the death of the patient. Histologic study of the left eye, enucleated for secondary glaucoma one year before, showed a diffuse disturbance of the reticuloendothelial cells of the type

which occurs in Hodgkin's disease. (7 figures, 7 references) Harry Horwich.

Van Allen, M. W. and Blodi, F. C. **Collateral circulation to the eye in occlusion of the internal carotid artery.** A.M.A. Arch. Neurol. **2**:74-79, Jan., 1960.

In view of the known collateral circulation from the external carotid to the ophthalmic artery on the same side, the authors question the "tonometic syndrome of Milletti," claimed to be diagnostic of internal carotid occlusion. The syndrome consists of three parts: 1. the systolic, retinal, arterial pressure (measured with the ophthalmodynamometer) is decreased on the side of the occlusion (the diastolic not regularly so), 2. the systolic retinal arterial pressure *is not* affected by compression of the common carotid on the same side, and 3. compression of the common carotid on the side opposite to the occlusion causes a decrease in the retinal systolic pressure on both sides but more markedly on the affected side. If the second part of this syndrome were true, it would cast doubt on the effectiveness of the collateral circulation from the homolateral external carotid artery. Six cases of internal carotid occlusion (five proved, one presumptive) were studied. Compression of the common carotid on the same side as the occlusion produced a significant lowering of the retinal systolic arterial pressure of the homolateral eye in five of the six cases. The authors conclude that the second part of Milletti's syndrome is incorrect. Lawrence T. Post.

19

CONGENITAL DEFORMITIES, HEREDITY

Pinkerton, O. D. **Bilateral anophthalmia.** A.M.A. Arch. Ophth. **63**:788-799, May, 1960.

A seven-month-old child without visible evidence of eyes or ocular tissue is described. Some light-senistive neural tissue may have been present deep in the orbits since there seemed to be a subjective response with intense light stimulation. (2 figures, 1 reference)

Edward U. Murphy.

Smith, J. L., Cavanaugh, J. J. A. and Stowe, F. C. **Ocular manifestations of the Pierre Robin syndrome.** A.M.A. Arch. Ophth. **63**:984-992, June, 1960.

This syndrome is characterized by three principal defects: micrognathia, cleft palate, and glossoptosis. Ocular involvement has not been previously reported and may consist of congenital glaucoma, retinal detachment, or high myopia. (10 figures, 12 references)

Edward U. Murphy.

Sorsby, Arnold and Wren, Norman. **A family group with asymptomatic macular defects inherited dominantly.** A.M.A. Arch. Ophth. **63**:918-922, June, 1960.

An asymptomatic macular lesion presumably present at birth and nonprogressive was found in seven members of a family and extended over three generations. Other known dominant disorders which begin with central lesions could be excluded, except, possibly, Best's disease. (5 figures, 8 references)

Edward U. Murphy.

20

HYGIENE, SOCIOLOGY, EDUCATION, AND HISTORY

Tower, Paul. **Carl Wedl. Histopathology of the eye in the nineteenth century.** A.M.A. Arch. Ophth. **63**:756-760. May, 1960.

This is a short essay on the life and significant work of this important but little known Viennese physician. His "Atlas of Pathological Histology of the Eye" (1861) was his most noteworthy publication and is quite readable even today. (5 figures, 22 references)

Edward U. Murphy.

NEWS ITEMS

Edited by DONALD J. LYLE, M.D.
411 Oak Street, Cincinnati 19, Ohio

News items should reach the editor by the 10th of the month. For adequate publicity, notice of postgraduate courses and meetings should be received three months in advance.

ANNOUNCEMENTS

POSTGRADUATE COURSE IN ATLANTA

The Department of Ophthalmology, Emory University School of Medicine, will sponsor a postgraduate course in ophthalmic surgery to be held on December 1st and 2nd, in the auditorium of the Grady Memorial Hospital, Atlanta, Georgia.

Dr. Frank D. Costenbader, senior attending and chairman of the Department of Ophthalmology, Children's Hospital, and senior attending ophthalmologist, Washington Hospital Center, Washington, D.C.; Dr. John M. McLean, professor of ophthalmology, Cornell University School of Medicine, New York; and Dr. Harold G. Scheie, professor of ophthalmology, University of Pennsylvania School of Medicine, Philadelphia, will be the guest lecturers.

Diagnostic principles and techniques, preoperative and postoperative management, and surgical principles and techniques in extraocular muscle surgery, cataract surgery, and glaucoma surgery will be discussed by this distinguished faculty.

SYRACUSE POSTGRADUATE COURSE

The Department of Ophthalmology of the State University of New York Upstate Medical Center at Syracuse will present its 11th annual postgraduate course in ophthalmology at the Hotel Syracuse, Friday and Saturday, December 2nd and 3rd. The following lecturers will participate: Dr. Howard Naquin, Dr. Raymond L. Pfeiffer, and Dr. John W. Henderson.

The tuition fee is $25.00, payable to the State University of New York Upstate Medical Center at Syracuse, 766 Irving Avenue, Syracuse 10, New York. This fee covers tuition, daily luncheons, and dinner on Friday night. The course is limited to 60 members. These will be accepted in the order in which applications, accompanied by checks, are received. Inquiries regarding the course may be addressed to James L. McGraw, M.D. at the same address.

SYMPOSIUM ON STRABISMUS

The New Orleans Academy of Ophthalmology announces a symposium on strabismus to be held during its annual mid-winter convention on February 19 to 24, 1961, at the Roosevelt Hotel, New Orleans. Members of the panel will be Drs. David Cogan, Goodwin Breinin, Arthur Jampolsky, John Henderson, Edmond Cooper, Marshall Parks, and Harold Brown. The registration fee of $75.00 includes associated membership in the academy for the year of 1961, as well as all other features of the convention. Hotel reservations should be made early by writing to the Executive Secretary, P. O. Box 469, New Orleans 1, Louisiana.

THIRD INTERNATIONAL COURSE

The third international course in ophthalmology of the Instituto Barraquer will be held from May 1 to May 5, 1961, in Barcelona, in the Avenida Palace Hotel; Avenida José Antonio 605. Registration is limited to 300. On the program will be a symposium on surgery of the crystalline lens and intraocular plastic lenses, and a symposium on surgery of the cornea. The complete program will be mailed before the beginning of the course to all those enrolled.

During the morning sessions, symposiums will be given. The different authors will give a short survey on the most important points of their papers. This will be followed by a round-table discussion in which each member of the panel can ask or answer questions and project films or slides. Members of the audience who wish to ask questions should present them in writing to the moderator at the beginning of the session. The fundamental conclusions will be summarized by the moderator at the end of the session. Simultaneous translation from and into the official languages of the course will be provided for the scientific sessions (Spanish, French, English).

For the afternoon sessions various courses have been scheduled and the members may choose whatever interests them most. There will be televised surgical sessions, clinical sessions with presentations of patients, and projections of films.

For further information write: Secretary, Instituto Barraquer, Laforja 88, Barcelona, Spain.

XIXTH INTERNATIONAL CONGRESS

The XIXth International Congress of Ophthalmology will be held at New Delhi, India, December 3 to 7, 1962. The subjects for reports and symposia are:

Reports—(1) "Tropical parasitical diseases of the eye," (Speakers): Prof. B. N. Bhaduri (Calcutta), Prof. Cyro de Rezende (São Paulo), Prof. A. Larmande (Algiers). (2) "Corneal degenerations," (Speakers): Prof. G. B. Bietti (Rome), Prof. A. G. Leigh (London), Prof. A. Edward Maumenee (Baltimore). Others may take part in discussion.

Symposia—(1) "Complications of cataract operation," Prof. L. Paufique (Lyons), chairman,

Prof. H. D. Dastoor (Bombay), and others to be selected by Prof. L. Paufique; (2) "Eales' disease," Prof. L. P. Agarwal (New Delhi), chairman; (3) "Electronic microscopy in ophthalmology," Prof. J. François (Ghent), chairman; (4) "Ophthalmological problems caused by the progress of aviation," Prof. Conrad Berens (New York), chairman.

A complete brochure containing information on symposia, reports, films, accommodation, cultural program, banquet, tours and itineraries is now under preparation and will be dispatched by November, 1960, to members who have sent their cards. The hotel accommodations will be arranged according to wishes of the members by the organizers at Delhi. For any other specific information which a member may desire communicate with, the Secretary General, Dr. Y. K. C. Pandit, Bombay Mutual Building, Sir P. M. Road, Bombay 1, India.

Miscellaneous

Receive award

The Ramon Magsaysay Foundation of the Philippines has awarded a prize of $10,000.00 to Sir Henry Tristam Holland, M.D., and his son, Ronald Holland, M.D., of Pakistan for their work as ophthalmic surgeons in caring for many thousands of nomadic tribesmen and the poor of Pakistan. The father and son team of British missionary ophthalmologists have performed over 150,000 eye operations during the last 59 years, and it is good to see that their noble work is recognized.

Advisory committee

Two additional members have joined the Advisory Committee of the National Council to combat Blindness, Inc., "The Fight for Sight." They are: Goodwin M. Breinin, M.D., chairman, Department of Ophthalmology, New York University-Bellevue Medical Center, and Harold G. Scheie, M.D., chairman, Department of Ophthalmology, University of Pennsylvania, School of Medicine.

Other members of the committee are: Charles A. Perera, M.D., chairman, Scientific Advisory Committee and associate professor of ophthalmology, Columbia University, College of Physicians and Surgeons; James H. Allen, M.D., chief, Department of Ophthalmology, Tulane University, School of Medicine, New Orleans; Bernard Becker, M.D., head, Department of Ophthalmology, Washington University, School of Medicine, Saint Louis; Hermann M. Burian, M.D., Department of Ophthalmology, State University of Iowa, College of Medicine, Iowa City; Frederick Crescitelli, Ph.D., Department of Zoology, University of California; Arthur Gerard DeVoe, M.D., director, Institute of Ophthalmology, The Presbyterian Hospital, New York; Dan M. Gordon, M.D., Department of Ophthalmology, New York Hospital-Cornell Medical Center, New York.

W. Morton Grant, M.D., Howe Laboratory of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard University Medical School, Boston; Charles Haig, Ph.D., Department of Physiology and Pharmacology, New York Medical College, Flower and Fifth Avenue Hospitals, New York; Michael J. Hogan, M.D., director, Francis I. Proctor Foundation for Research in Ophthalmology, University of California Medical Center, School of Medicine, San Francisco; V. Everett Kinsey, Ph.D., assistant director for research, Kresge Eye Institute, Detroit; Peter C. Kronfeld, M.D., head, Department of Ophthalmology, University of Illinois, College of Medicine, Chicago; Irving H. Leopold, M.D., director of research, Wills Eye Hospital, Philadelphia; A. Edward Maumenee, M.D., director, Wilmer Ophthalmological Institute, The Johns Hopkins Hospital, Baltimore; John M. McLean, M.D., chief, Department of Ophthalmology, New York Hospital-Cornell Medical Center, New York; Stuart Mudd, M.D., Department of Microbiology, University of Pennsylvania, Philadelphia; Frank W. Newell, M.D., chairman, Section of Ophthalmology, Department of Surgery, University of Chicago, Chicago; Edward W. D. Norton, M.D., chairman, Department of Ophthalmology, Jackson Memorial Hospital, University of Miami, School of Medicine, Miami; Theodore C. Ruch, Ph.D., chairman, Department of Physiology and Biophysics, University of Washington; Samuel L. Saltzman, M.D., Department of Ophthalmology, New York Medical College, Flower and Fifth Avenue Hospitals, New York; George K. Smelser, Ph.D., director of research, Department of Ophthalmology, Columbia University, College of Physicians and Surgeons, New York; Bradley R. Straatsma, M.D., chief, Division of Ophthalmology, Department of Surgery, University of California Medical Center, School of Medicine, Los Angeles; Kenneth C. Swan, M.D., chief, Department of Ophthalmology, University of Oregon, Medical School, Portland; Phillips Thygeson, M.D., Francis I. Proctor Foundation for Research in Ophthalmology, University of California Medical Center, School of Medicine, San Francisco.

Societies

District of Columbia

The Section of Ophthalmology, the Medical Society of the District of Columbia, announces that meetings for the 1960-1961 season are scheduled for October 25th, December 13th, and February 14th, with the date of the April meeting to be announced later.

Elbert W. Dodd, Jr., M.D., is president of the society; Paul E. Zehfuss, M.D., vice president in charge of program; and Henry L. Bastien, M.D., secretary-treasurer.

Milwaukee society

Dr. Alston Callahan, Birmingham, Alabama, was guest speaker at a recent meeting of the Milwaukee Oto-Ophthalmic Society. The subject of his address was "Plastic lid surgery for ophthalmologists." Newly elected officers of the society are: Roger Lehman, M.D., president; George J. Roncke, M.D., vic president; Charles J. Finn, M.D., secretary-treasurer.

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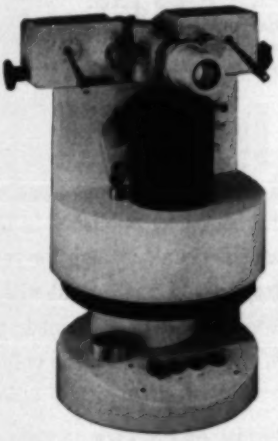

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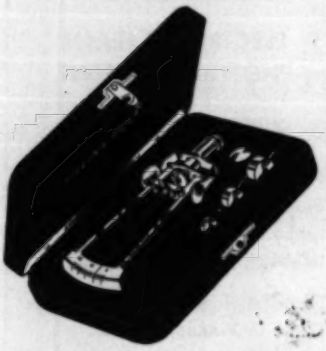

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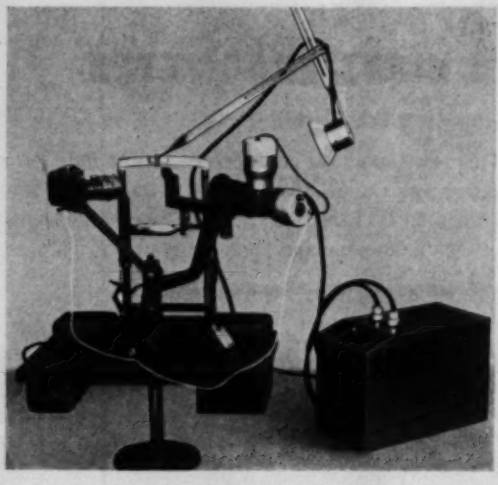

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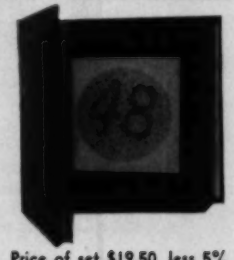

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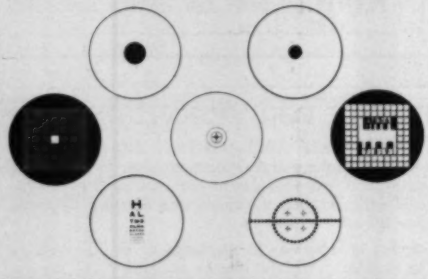

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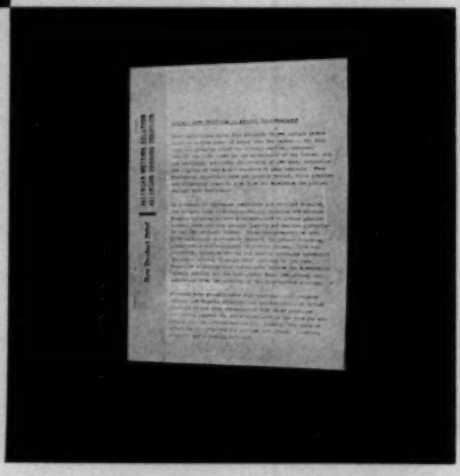

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